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Human and Animal Physiology

Innovative Drugs for Curie Temperature-Controlled Highly Localized Tumor Therapy

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Abstract. Cardiovascular diseases and cancer remain the leading causes of global morbidity and mortality. In 2023, they were responsible for approximately 35% and 24% of all deaths worldwide, respectively. Cardiovascular diseases and cancer reveal a bidirectional association and demonstrate a significant super-additive impact on each other. Combination cancer therapies effectively target and affect pathways that play important role in causing and sustaining malignant cell induction and progression. Alkali metal solutions are among the intensively studied anticancer agents, whereas cesium chloride is a popular alternative anticancer BAD highly (often – uncontrolled) consumed in USA. The results of the reported research clearly show that rubidium chloride solution reveals the highest biological efficacy and selectivity to cancer cells compared to other tested samples, which is rather difficult to interpret in the frame of the "high pH cancer therapy" concept. The next stage of the research should focus on measuring alkalinity and alkali metal content in the intracellular and intercellular areas of the exposed cells. © *2026 Bull. Natl. Acad. Sci. Georg.*

Keywords: combined therapy of cancer, drug selectivity, alkali metal solutions, cell viability, MTT testing, "high pH therapy" concept

Introduction

Cardiovascular diseases and cancer remain the leading causes of global morbidity and mortality, accounting responsible for approximately 35% and 24% of deaths, in 2023 respectively. Globally, the major cancer types are lung, breast and colorectal cancers, whereas the non-small cell lung cancer (NSCLC) is the most hazardous form of the lung cancer. Cardiovascular disease and cancer are known to reveal a bidirectional association and demonstrate a significant super-additive impact on each other. The World Health Organization (WHO)'s cancer agency and the International Agency for Research on Cancer (IARC) predict an almost 80% increase of new cancer cases from 20 million cases in 2022 to estimated 35 million cases by 2050. Cancer burden grows dramatically due to a lot of environmental risks, population aging, chemical and radioactive pollution due to the testing of nuclear weapons, striking economic and social differences between different countries and segments of the population, etc., as well as due a new level of accelerated development of nuclear power stations and the concomitant increase in the volume of active and spent nuclear fuel. Therefore, there is an urgent need to increase the biological effectiveness and safety of cancer therapy modalities. As is known, proton therapy (PT) is the most advanced type of particle therapy of malignant neoplasms. Despite its noticeably lower relative biological effectiveness (RBE) in comparison to the C-ion therapy, proton therapy is much more demanded due to significantly higher cost, high research intensity and very high requirements for medical and engineering personnel of the C-ion therapy. According to PTCOG data *(Particle Therapy Co-Operative Group, 2024)*, outspread of proton therapy is currently much higher than of the heavy ion therapy. In turn, the outspread of PT is noticeably lower than was expected in 2018 taking into account the overall super-linear growth of the PT facilities commissioned, being under construction or in a planning stage. The literature data clearly show that the overall spread of hadron therapy has also slowed down drastically. As of 2021, there were 107 operating proton therapy facilities, with 26 under construction and only 11 in the planning stage. At the same time, there were only 13 operating C-ion therapy centers, while 6 were under construction and only 1 was in the planning stage. Therefore, in our opinion, significant increase of the biological effectiveness and safety of proton therapy is an acute and urgent need of the current day.

Combination therapy of cancer, often called the “cornerstone” of malignant tumor treatment, effectively targets and affects pathways that play important roles in causing and sustaining malignant cell induction and progression. An evidently successful modality of combination therapy of cancer was reported in in the sixties of the last century (Freireich et al., 1965), while the modern concept of the combination therapy of cancer in its whole body (Yagawa et al., 2017) and strongly localized (Chirakadze et al., 2018) modifications was developed in the period of 2017-2022. Synergistic effects can play an important positive or negative role in combination therapy as they can increase the effectiveness and safety of the therapeutic effect, or vice versa, drastically decrease treatment efficacy, increase toxicity to healthy cells and cause or enhance undesirable side effects in a super-additive, additive or antagonistic manner (Jishiashvili et al., 2019; Mitagvaria et al., 2020; Chirakadze et al., 2021a; Chirakadze et al., 2021b; Khorshid et al., 2011; Mitagvaria et al., 2023). Therefore, comprehensive study of the “positive” and “negative” additive and antagonistic toxicity is of particular importance for the successful development of new modalities within the concept of combination therapy and correct choice of of application methods. Applied doses of nanoparticles can be crucial to achieve maximum therapeutic efficacy and safety.

Background and necessity of the research and rationale for component selection. The first stage of our research, aimed to develop a number of new combination drugs based on the concept of the strongly localized combined cancer therapy, included a comprehensive review of the literature on the anticancer effectiveness, mechanisms, safety (therapeutic window and therapeutic value), synergy and the general and specific toxicity of the widely used chemotherapeutic drugs, cesium and rubidium chloride and carbonate solutions (well known as putative anticancer agents) and DMSO (a widely used solvent which potentiates a big number of chemicals to penetrate into intercellular and intracellular fluids, accelerating and enhancing their therapeutic effect).

Currently, cesium and rubidium chlorides and carbonates are widely used (often without any medical approval or supervision) as alternative anticancer agents and can lead to severe cardiac dysfunctions including sudden cardiac arrest (Blagosklonny, 2005; Khdair et al., 2010; Gottesman et al., 2002; Hanahan et al., 2000; Girigoswami & Girigoswami, 2023). On the other hand, according to the so called "high pH cancer therapy" concept, solutions of cesium and rubidium, as well as other solutions of alkali metals, can significantly change the alkalinity of the intracellular area and microenvironment, thereby improving the reverse pH gradient, a hallmark of cancer metabolism, manifested by extracellular acidosis and intracellular alkalization.

Therefore, to answer the question, whether the "high PH cancer therapy" concept really corresponds to reality, we must know where (in the intracellular region or in the surrounding microenvironment) alkali metal ions accumulate and which salts (chlorides or carbonates) have higher anti-cancer biological activity. According to the above high-pH concept, cesium and rubidium carbonates should have significantly higher anticancer efficacy than cesium and rubidium chlorides.

Experimental

In order to characterize the anticancer biological efficacy and safety of cesium and rubidium chlorides and carbonates we developed four putative anticancer solutions (see Table) by means of standard mechanical and ultrasound agitation equipment. MTT testing of the viability of A549 NSCLCc (non-small cell lung cancer cells) an NHDFc (normal human dermal fibroblast cells) exposed to the developed mixtures was carried out using chemicals and methods described in papers (Khorshid et al., 2011; Mitagvaria et al., 2023).

The measured viability dose/response curves characterize the biological efficacy of the tested mixtures against the exposed cancer and healthy cells, while the safety of the mixtures should be characterized by the ratio of viability of exposed healthy NHDF cells to the viability of the exposed cancer A549 cells, which can serve as an indicator of the expected therapeutic window or an index of the specific selectivity (S) of the tested combinations to cancer cells in comparison to healthy cells. Testing of each sample was carried out in five replications and the square median error (SME) was calculated.

Table. Chemical content and total volume of the developed and tested samples

Components	Molar content in solution, millimoles	Total volume of liquid, ml
Cesium chloride CsCl	144	50
Saline solution (0.9%)	The rest	
Cesium carbonate Cs_2CO_3	144	50
Saline solution (0.9%)	The rest	
Rubidium chloride Rb Cl	144	50
Saline solution (0.9%)	The rest	
Rubidium carbonate Cs_2CO_3	144	50
Saline solution (0.9%)	The rest	

Results and Discussion

Results of MTT testing and calculating of the specific selectivity for each developed combination are given in Figs. 1-4.

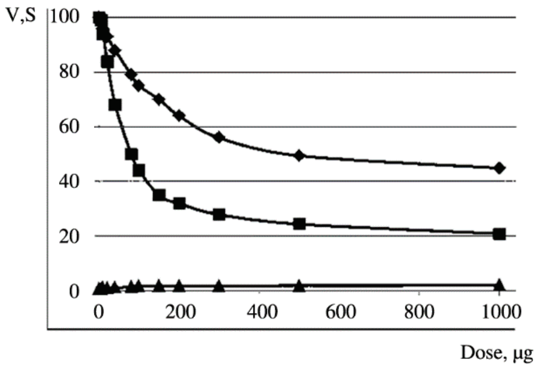

Fig. 1. Cell viability (V) and specific selectivity (S) of test sample 1, cesium chloride (from up to bottom: NHDF, A549, S).

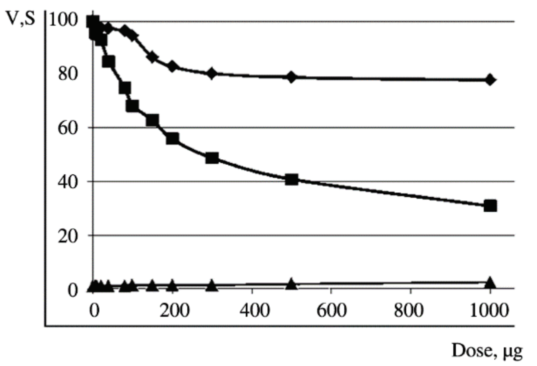

Fig. 2. Cell viability (V) and specific selectivity (S) of test sample 2, cesium carbonate (from top to bottom: NHDF, A549, S).

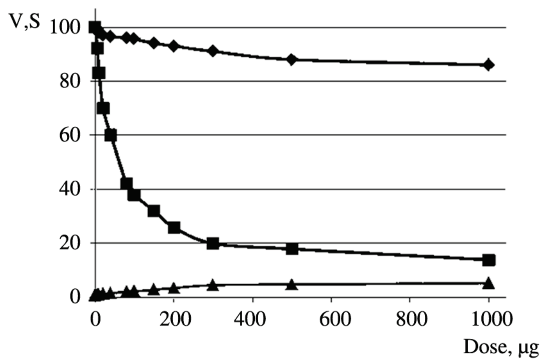

Fig. 3. Cell viability (V) and specific selectivity (S) of test sample 3, rubidium chloride (from up to bottom: NHDF, A549, S).

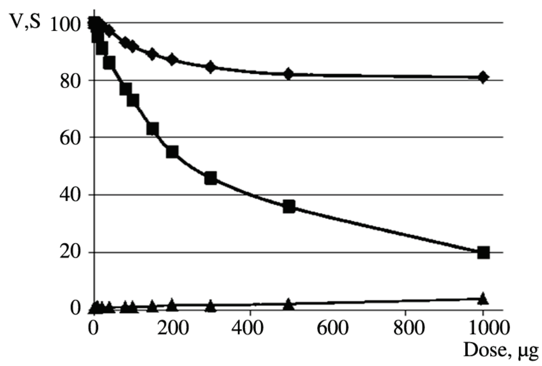

Fig. 4. Cell viability (V) and specific selectivity (S) of test sample 4, rubidium carbonate (from top to bottom: NHDF, A549, S).

The data in Figs. 1-4 clearly show that rubidium chloride solution (sample 3) reveals the highest biological efficacy and selectivity to cancer cells among the four tested samples, and it is rather difficult to interpret the obtained data on the efficacy and selectivity of samples in the frame of the “high pH cancer therapy” concept. The next stage of the research should be focused on measurement of the alkalinity and alkali metal content in intracellular and intercellular areas of the exposed cells.

ადამიანისა და ცხოველთა ფიზიოლოგია

ინოვაციური სამკურნალო პრეპარატები სიმსივნეების კიურის ტემპერატურით კონტროლირებადი ძლიერად ლოკალიზებული კომბინირებული თერაპიისთვის

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გულ-სისხლძარღვთა დაავადებები და კიბო გლობალური ავადობისა და სიკვდილიანობის ძირითადი მიზეზია. გამოვლენილია გულ-სისხლძარღვთა დაავადებებსა და კიბოს შორის მნიშვნელოვანი (ხშირად – სუპერადიტიური) ურთიერთკავშირი. კიბოს მრავალკომპონენ-ტიანი კომბინირებული თერაპია არის კიბოს მკურნალობის შედარებით ახალი მაღალ-ეფექტიანი და უვნებელი სახეობა, რომელიც კომპონენტების სწორად შერჩევისა და ოპტი-მალური დოზირების შემთხვევაში შეიძლება რამდენჯერმე უფრო ქმედითი და უვნებელი იყოს მონოთერაპიასთან შედარებით. ტუტე ლითონის ხსნარები აქტიურად შეისწავლება როგორც კიბოს საწინააღმდეგო პოტენციური საშუალება, ხოლო ცეზიუმის ქლორიდი ფარ-თოდ არის გაცრცელებული როგორც ალტერნატიული ანტისიმსივნური ბიოლოგიურად აქტიური საშუალება, რომელიც დიდი რაოდენობით (ხშირად სრულიად უკონტროლოდ) მოიხმარება ამერიკის შეერთებულ შტატებში. წარმოდგენილი კვლევის შედეგები ნათლად აჩვენებს, რომ ოთხ ტესტირებულ ნიმუშს შორის რუბიდიუმის ქლორიდის ხსნარი ავლენს უმაღლეს ბიოლოგიურ ეფექტიანობას და კიბოს უჯრედების მიმართ სელექტიურობას, რაც რთულია აიხსნას „მაღალი pH-ით კიბოს თერაპიის“ კონცეფციის ფარგლებში.

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