Submitted: 17.05.2023
Accepted: 03.10.2023
Early publication date: 05.12.2023

Endokrynologia Polska
DOI: 10.5603/ep.95505
ISSN 0423–104X, e-ISSN 2299–8306
Volume/Tom 74; Number/Numer 6/2023

A new antiviral hypothesis and radioactive iodine therapy to other cancers, such as breast cancer, lung cancer, and glioblastoma multiforme (GBM)?

Agata Czarnywojtek[1, 2*#], Paweł Gut[2*], Magdalena Borowska[1*], Nadia Sawicka-Gutaj[2], Paweł Caputa[3], Beata Kos-Kudła[4], Marek Ruchała[2], Alfio Ferlito[5#]

[1]*Department of Pharmacology, Poznan University of Medical Sciences, Poznan, Poland*
[2]*Chair and Department of Endocrinology, Metabolism and Internal Medicine, Poznan University of Medical Sciences, Poznan, Poland*
[3]*Department of Oncology, Greater Poland Cancer Centre, Poznan, Poland*
[4]*Department of Endocrinology and Neuroendocrine Tumours, Department of Pathophysiology and Endocrinology, Medical University of Silesia, Katowice, Poland*
[5]*Coordinator of the International Head and Neck Scientific Group, Padua, Italy*
**The author (as a GM) contributed to this work.*
[#]This paper was written by members and invitees of the International Head and Neck Scientific Group (www.IHNSG.com).

Abstract
Radioactive iodine therapy (RIT) is an effective, safe, and cheap method in benign and malignant thyroid diseases. There is still an unresolved question of whether RIT treatment also plays a role in the treatment of, for example, breast cancer, lung cancer, or glioblastoma multiforme (GBM). These studies are currently being carried out in rats in combination with genes, but it may be an interesting challenge to assess "pure" RIT alone, thanks to the expression of sodium iodide symporter (NIS), is effective in other organ nodules, both benign and malignant. Cloning of the NIS in 1996 provided an opportunity to use NIS as a powerful theranostic transgene. In addition, NIS is a sensitive reporter gene that can be monitored by high-resolution PET imaging using the radiolabels [^{124}I]sodium iodide ([^{124}I]NaI) or [^{18}F] tetrafluoroborate ([^{18}F]TFB). Based on published positron emission tomography (PET) results, [^{124}I]sodium iodide and internally synthesized [18F]TFB were compared in an orthotopic animal model of NIS-expressing glioblastoma. The results showed improved image quality using [^{18}F]TFB. Based on these results, we will be able to extend the NIS gene therapy approach using non-viral gene delivery vehicles to target orthotopic tumour models with low-volume disease such as GBM. Is it possible to treat RIT alone without using the NIS gene in GBM? After all, the NIS symporter was detected not only in the thyroid gland, but also in different tumours. The administration of RIT is completely harmless; the only complication is hypothyroidism. Indeed, recently it has been shown that, for example, in the case of thyroid cancer, the maximum RIT is 37000 MBq (1000 mCi). When beneficial effects of therapy in GBM are not possible (e.g. neurosurgery, modulated electro-hyperthermia, chemotherapy, immunotherapy, cancer vaccines, or oncolytic viruses), could RIT provide a "revolution" using NIS? **(Endokrynol Pol 2023; 74 (6): 601–609)**

Key words: *sodium iodide symporter (NIS); glioblastoma multiforme (GM); gene therapy, RIT radioiodine treatment (RIT)*

Introduction

Radioactive iodine therapy (RIT) in benign and malignant thyroid diseases is very important thanks to the birth of nuclear medicine [1]. But can it play a role in the future, for example, in the treatment of brain tumours like glioblastoma multiforme (GM)? It should be noted that the sodium iodide symporter (NIS) plays the main role in the latest RIT. This underestimated NIS is nothing more than a protein responsible for the active transport of iodine to the thyroid cell. The NIS protein was discovered in the rat thyroid, and the sequence of the human NIS gene was determined in 1996 [2]. Spitzweg et al. [3] discovered the presence of NIS in extrathyroid tissues. Interestingly, this protein, as well as iodine, is responsible for the transport of many other ions, such as ClO3–, SCN–, SeCN–, NO3–, Br–, BF4–, IO 4–, BrO 4–, SO 4–, F–, HPO4–2, and ReO4– [4].

The function of NIS as a protein located in the membrane of thyroid follicular cells

NIS is a cell membrane glycoprotein located in the basolateral membrane of the thyroid follicular cells, mediating the active transport of iodide to the thyroid, which is an important condition for the biosynthesis of thyroid hormones [5, 6]. NIS-mediated iodide transport can be inhibited by competitive inhibitors, thiocyanate

Magdalena Borowska, PhD, Poznan University of Medical Sciences, Department of Pharmacology, Rokietnicka 3 Street, 60–806 Poznan, Poland, tel: +48 61 6418326; e-mail: mborowska@ump.edu.pl

and perchlorate, as well as by the Na+Ka+-ATPase inhibitor ouabain [7]. The functional expression of NIS is the basis for the diagnostic and therapeutic use of radioactive iodide, which has been widely used in the treatment of differentiated thyroid cancer for 80 years [8]. The cytoreductive effect of NIS-mediated targeted radioisotope therapy is related to the so-called "cross-effect", i.e. the impact through particle decay of the build-up of radioisotope radiation in NIS-expressing cells on neighbouring cells that do not express NIS [9]. In addition to radioiodide, alternative radionuclides, such as the beta emitter 188Re or alpha emitter 211At, are transported by NIS [10–13]. By successfully cloning the NIS cDNA in 1996, Dai et al. [2] produced a new and well-proven dual function tool to enable image-guided selective NIS gene transfer to non-thyroid tumours. Next, therapeutically effective radionuclides were shown to be successful in restoring radioiodide accumulation both in vitro and in vivo after stable ex vivo transfection of rat thyroid cells (FRTL-Tc) transformed with rat NIS cDNA [2, 9, 14].

The role of the NIS protein in the thyroid gland

The NIS polypeptide chain is arranged in a spiral through the cell membrane. There are 13 transmembrane segments and 14 extramembrane segments, including terminal fragments with the NH2 end located extracellularly and the COOH end located intracellularly. There are 3 potential glycosylation sites for the NIS protein: one is in the seventh extramembrane domain and the other 2 are in the 13th extramembrane domain. It has been proven that the level of glycosylation of the NIS protein does not affect its activity, stability, or location in the cell membrane [14]. The NIS protein is found in about 20–30% of normal thyroid follicular cells [7, 15–17] and shows the diversity of its existence both within the thyroid follicles and within the thyrocytes of a given follicle [7, 15]. There is greater symporter expression observed in the small and medium-sized follicles made of cylindrical and cubic cells, considered hormonally active, than in the flat thyrocytes that form large follicles [15–17]. The expression of the NIS protein in the thyroid tissue is subject to complex regulation and depends on many factors, including transcription factors, enhancers in the NIS gene, oncogenes, cytokines, growth factors, hormones, antibodies, and some drugs [18].

Thyroid-stimulating hormone in NIS regulation

The most important regulator of NIS protein activity in thyroid cells is thyroid stimulating hormone (TSH), whose effect on the sodium-iodine symporter is cAMP-dependent [19]. Thyrotropin stimulates the expression of thyroid transcription factors (i.e. transcription factor 1 and 2 [TTF1, TTF2] and PAX-8), which in turn stimulate expression of the following genes: thyroglobulin, thyroperoxidase, TSH receptor, and sodium-iodine symporter [18, 20, 21]. Thyrotropic hormone not only increases the biosynthesis of the sodium-iodine symporter but is also an essential factor in making sure the NIS protein is correctly localised in the cell membrane [22]. It has been noted that in the absence of TSH, the half-life of NIS protein degradation shortens from 5 to 3 days, with the amount of NIS protein decreasing faster in the cell membrane than in the cytoplasm. This suggests that when the influence of TSH is removed, the NIS protein moves from the cell membrane to intracellular compartments and is unable to transport iodine [22]. TSH in the cAMP-dependent mechanism probably affects the post-transcriptional phosphorylation of the NIS protein [23], which may play a role in how the symporter is distributed intracellularly [22]. Phosphorylation is a known cellular mechanism that modulates the activity, intracellular localisation, and/or degradation of proteins [11]. It may occur in the absence of TSH, but then the phosphorylation sites in the NIS protein are different to those when in the presence of TSH [22].

Iodine, thyroglobulin, and NIS symporter

Iodine and thyroglobulin, which show an autoregulatory effect on iodine uptake in the thyroid, reduce the level of expression of the NIS protein [24–28]. The effect of externally administered iodine depends on the dose. An inadequate supply of iodine increases the sensitivity of thyrocytes to the stimulating effect of TSH, which increases iodine uptake. However, as the amount of iodine administered increases, the process of its organisation is inhibited, which causes the acute Wolff-Chaikoff effect [29]. This effect is short-term, and as the thyroid gland adapts to the continued influx of iodine, thyroid hormone synthesis returns almost to normal, which is called an escape from the acute Wolff-Chaikoff effect [30]. As a result of studies in which iodine administration suppressed the thyroid mRNA concentration of the NIS gene [24] and/or decreased the concentration of the NIS protein [31, 32], it has been suggested this escape from the acute Wolff-Chaikoff effect is caused by a decrease in the degree of expression and NIS protein activity. This reduces the intrathyroid iodine concentration below the critical limit, which allows the maintenance of iodine organisation [32, 33].

The role of cytokines in NIS

Cytokines such as interleukin 1 (IL-1), tumour necrosis factor alpha (TNF-α), and interferon gamma (INF-γ) inhibit NIS gene expression and the uptake of iodine in the rat thyroid cell line (FRTL-5, Fischer rat thyroid

line-5) as well as in human thyrocytes [34, 35]. Reducing the NIS gene expression, these cytokines, which are produced in inflammatory infiltrates, may play a role in the development of autoimmune hypothyroidism [34]. In addition, by suppressing the expression of the symporter, cytokines may cause attenuation of the effect caused by antibodies stimulating the TSH receptor in Graves' disease [36]. This could explain, at least partially, the lack of correlation between the concentration of antibodies stimulating the TSH receptor and the clinical severity of hyperthyroidism in this disease [36]. Antithyroid drugs such as methimazole or propylthiouracil are mentioned among the external factors that reduce the expression of the NIS protein [31].

Exogenous factors affecting NIS (drugs and RITs)

Among the external factors that reduce the expression of the NIS protein, antithyroid drugs such as methimazole or propylthiouracil are mentioned [31]. The clinical effect of the negative effect of thyrostatics on the NIS protein is the lower effectiveness of radioactive iodine treatment in patients who previously received thyrostatics [36–40].

The factors influencing the expression of the NIS protein also include those whose activity has been proven only in the studies of the FRTL-5 cell line, and they include, among the inhibitors — cytokine transforming growth factor beta 1 (TGF-β1) and IL-6, ceramides and sphingomyelinase, triiodothyronine, dexamethasone, and oestradiol, and among the inducers — adenosine [31, 33, 41, 42].

Application of NIS in glioblastoma multiforme imaging and therapy

The role of NIS imaging in glioblastoma multiforme

Glioblastoma (GBM) is the most common primary brain tumour with poor prognosis, and it is mainly treated with palliative therapy. Several mechanisms are used by this highly complex tumour to evade treatment, which means new GBM treatment strategies are urgently required [43]. The blood-brain barrier (BBB), which can block radiotracers and gene vectors, is one reason for the limitations in effective treatment and detection of GBM. Because NIS-mediated radionuclide imaging and therapy do not require complicated radiolabelling procedures, the small-size radionuclides used are able to penetrate the BBB and diffuse into the tumour [44].

Several preclinical studies have demonstrated the potential use of NIS in GBM imaging and therapy. A study by Cho et al. [45] used a rat model with F98 intracerebral gliomas that were retrovirally transduced with human NIS. The authors demonstrated the possibility of non-invasive imaging of GBM using by [^{99m}Tc]pertechnetate- and [^{123}I]NaI-scintigraphy, and then prolonging the survival time of rats after ^{131}I therapy. Guo et al. [44] published imaging and therapy experiments with ^{188}Re or ^{131}I in mice with tumour xenografts injected with the U87 human glioblastoma cell line that had been transfected with a recombinant lentiviral vector containing human NIS in the right armpit. In vivo imaging results, assessed by gamma camera imaging, showed the ^{188}Re/^{131}I accumulated in the NIS-containing tumours, and effective reduction of the tumour volume was achieved in the ^{188}Re or ^{131}I treated mice compared to untreated control mice. In another study, using one of the most extensively studied oncolytic viruses for NIS gene transfer, Opyrchal et al. [46] demonstrated the effectiveness of the [^{123}I]NaI or [^{99m}Tc]pertechnetate gamma camera or micro-single-photon emission tomography/computed tomography (microSPECT/CT) *s.c.* imaging and orthotopic murine glioblastoma xenografts after intratumoural infection with measles virus encoding NIS (MV-NIS) to induce NIS expression in brain tumour tissue. Combined radiovirotherapy with MV-NIS and ^{131}I resulted in improved antitumour activity and survival compared to viral therapy alone in both cases of GBM.

The advantage of PET, as opposed to scintigraphy or SPECT, is the potentially more accurate detection of small-volume GBM lesions with a relatively low level of NIS expression when systemic gene transfer methods are used [47]. Preclinical imaging studies with [^{18}F]TFB as a PET tracer were performed in athymic mice with C6 human glioma expressing NIS *s.c.* tumour xenografts producing adventurous tumour uptake of [^{18}F]TFB via NIS [48]. Recently, Kitzberger et al. [49] used the U87 human glioblastoma cell line stably transfected with a plasmid expressing NIS (CMV-NIS-pcDNA3) (U87-NIS) to track tumour expression of NIS *s.c.* and orthotopic brain tumours. Using this, they made a direct comparison of ^{124}I and [^{18}F]TFB as radiotracers for PET imaging of small animals. The localisation of the NIS protein on the cell membrane of the U87-NIS cells and its active transport of iodide was confirmed by immunocytochemistry and [^{125}I]iodide uptake assays in vitro. Very interestingly, these U87 tumours revealed endogenous NIS-mediated ^{123}I uptake, in addition to the thyroid gland, which was observed in other organs such as the stomach, salivary glands, and in the bladder due to renal excretion [50]. In our opinion, it would be interesting to check the endogenous NIS-mediated ^{123}I uptake when assessing GM tumours.

In a second group of mice, NIS-based radionuclide biodistribution was investigated using 3D preclinical PET scanners after an intravenous injection of [^{124}I]NaI or [^{18}F]TFB. The results showed a high accumula-

tion of NIS PET markers in the U87-NIS tumours [51]. In these animals, the physiological signal of organs endogenously expressing NIS (thyroid, mammary glands, salivary glands, stomach), and tumour uptake was effectively blocked [50]. Kitzberger et al. [49] showed the possibility of PET imaging by monitoring the expression of the NIS gene in these brain tumours. They conducted the study based on a mouse, an appropriate orthotopic model. Nude mice with U87-NIS orthotopic brain tumours received [^{124}I]NaI or [^{18}F] TFB for PET imaging. Both radiopharmaceuticals caused NIS-mediated accumulation of radionuclides in the brain tumours, which was comparable to [^{124}I] NaI- and [^{18}F]TFB-PET [50].

The NIS gene therapy concept for glioblastoma multiforme

Future prospects: non-viral systemic NIS gene delivery to glioblastoma multiforme

The potential of NIS as a theranostic gene and the improvement of new gene delivery systems have broadened the possibilities of using the NIS gene therapy concept for extrathyroidal tumours [9, 51]. Based on the gene therapy approaches summarised above, the preclinical development of the NIS gene therapy approach will be extended to other aggressive non-thyroid cancers in the future, such as GBM, with the primary objective being a phase I/II clinical trial.

The efficacy of non-viral systemic NIS gene delivery systems based on mesenchymal stem cells or synthetic polyplexes to target glioma and using advanced [^{124}I] NaI and [^{18}F]TFB in animals — PET imaging has been reported [52, 53]. Spellerberg et al. [53] addressed tumours of mice that received non-targeted mono DBCO-PEG24/NIS polyplexes, which exhibited an uptake of 1.96 ± 0.52% ID/mL. Vadysirisack et al. [54] studied doxycycline-induced NIS expression that was established in cell lines of various tissue types, including human (FTC133 thyroid cancer cells), HeLa human (cervical cancer cells), and rat (PC12 pheochromocytoma cells).

There is a double benefit to NIS gene transfer: it is therapeutic and enables imaging of transgenic protein expression [45]. Until now, evaluating the expression of a transgenic protein required an invasive biopsy or even the death of the animal undergoing gene therapy. Meanwhile, using NIS gene transfer may enable non-invasive and reproducible visualisation of vector expression, which may be an important tool in preclinical and clinical gene therapy trials [45, 54]. The use of the NIS gene as a vector transfer monitoring gene (imaging reporter gene, Imagene) makes it possible to assess both the location and concentration and duration of expression of the transgenic protein [45, 54]. Gene therapy using the NIS gene, however, requires the resolution of several issues, including whether the post-translational processes, including the distribution of the NIS protein to the cell membrane, affect iodine uptake in cells expressing the exogenous symporter [54]. As many studies have shown, the cellular distribution of the symporter is a disorder-prone process and may, therefore, be a limiting factor for iodine uptake by the exogenous NIS protein. However, the study carried out in the FTC133, HeLa, and PC12 cell lines did not show distribution disorders of the transgenic NIS protein. In addition, the uptake of radioactive iodine by the exogenous NIS protein observed in many other cell types indicates that disturbances in the cellular distribution of the symporter do not play a role in the use of NIS gene transfer [54]. The problem of NIS gene therapy remains the inability of transfected cells of many tumours to retain iodine. Huang et al. [55] noted the limited effectiveness of the radioactive iodine destruction of non-small cell lung cancer cells transfected with the NIS gene due to the rapid elimination of ^{131}I. For comparative purposes, the study used a combined transfer of the NIS gene and the thyroperoxidase gene, which enables the organification and maintenance of iodine in the cell. This increased the effectiveness of the radiotherapy. However, as shown in other studies, the organification of iodine may not be a prerequisite for successful tumour radio ablation using the NIS gene [24, 56]. RIT reduced the tumour volume by more than 75% [57]. Meanwhile, there are no grounds to claim that prostate cells have the ability to organise iodine, if only because they do not initially capture iodine. However, gene therapy using the NIS gene to treat prostate cancer is potentially possible and requires further in vivo research. One study compared the human and rat NIS proteins by transducing retroviral vectors with the genes of these proteins into various human cancer cell lines and rodent cancer cells. It has been shown that the radioactive iodine concentration of the rat NIS protein is up to 5 times higher than that of the human, in both rodent and human cell lines [58]. The difference in the functionality of both symporters may result from the different structure of the rat and human NIS protein or from different regulatory mechanisms. Whether the rat NIS protein has a greater uptake ability for radioactive iodine in vitro only or also in vivo needs to be answered [58].

In addition, this study showed the differentiation of iodine uptake by the transgenic NIS protein in individual cancer cell lines. Therefore, further research is needed to assess which cancers will respond best to RIT after NIS gene transfer. Hence, the most important task for researchers is to transfer the knowledge gained in laboratories to clinical trials.

A new hypothesis of RIT treatment in GM

Is it possible to use ^{131}I alone without using the NIS gene? After all, the NIS symporter was detected not only in the thyroid gland, but also in different tumours. The administration of RIT is completely harmless, the only complication being hypothyroidism. However, there are contraindications and concerns regarding increased tumourigenesis in individuals undergoing ^{131}I treatment, as well as recommendations limiting procreation. Indeed, it has been shown recently that, for example, in the case of thyroid cancer, the maximum therapy is 1000 mCi. Or is it worth using RIT in an ablative dose of 800 MBq (22 mCi) of ^{131}I in an outpatient setting, with the possibility of repeating it? What do we have to lose? After all, GM patients live very short lives. And yet NIS gene expression was observed in GM, although only in animals.

As early as 1955, Amyes et al. [59] had already succeeded in pinpointing the location of brain tumours using radioactive iodine and phosphorus. A needle probe was used in this procedure for the first time, which proved to be very useful in quickly locating and defining the affected area.

Radioisotopes of various elements are now used with increasing frequency in nuclear medicine. This additionally proves that using RIT does not damage the skull. This is where beta rays, in addition to imaging, may be effective in RIT. It is not always possible to remove the whole GM, especially grade IV. Attention was also paid to the revolution in targeted (individual) therapy in the case of tyrosine kinase inhibitors (imatinib, sunitinib, and sorafenib) [60–64] and in the case of the latest drugs such as crizotinib, entrectinib, or larotrectinib [65, 66]. NanoTherm® therapy is also used in patients with GBM who have exhausted conventional treatment methods [67]. Recently developed individualised multimodal immunotherapy (IMI) is based on cancer vaccines [68–78] and oncolytic viruses [79, 80].

And maybe we could try using non-virology therapy in the form of RIT, even without genetic aspects – just classical therapy. As before, they turned to a completely new therapy. Just over 60 years ago, Amyes et al. [59] showed that some benign and malignant pathological disorders in the brain (e.g. inflammation, vascular disease, and, most importantly, tumours) tend to increase the rate at which certain ions pass through the so-called BBB (especially ^{131}I).

Or maybe we should just revolutionise and try to use RIT in GM. And what is very important, this therapy can be completely free, and even if not, it does not have to be very expensive. Hypothyroidism is just a "complication". But perhaps we are getting a new life, or perhaps patients already freed from GM.

Side effects of antithyroid drugs in non-standard therapy amiodarone-induced thyrotoxicosis

Similarly, we used and still use RIT in patients with amiodarone-induced thyrotoxicosis (AIT) with very low uptake (RAIU) [81] modelled on the publication of Hermida et al. [82] or of Gursoy et al. [83], whose RAIU was slightly elevated. But a preliminary study was the first in Poland to use RIT in euthyroid patients with a history of hyperthyroidism and permanent atrial fibrillation prior to the administration of amiodarone [84]. However, the authors of the study used very high radioiodine activities (up to 80 mCi ^{131}I), which are not routinely used in the treatment of hyperthyroidism. Based on our experience, RIT is relatively safe and leads to hypothyroidism [81, 84].

And in the case of AIT, when antithyroid drugs (ATDs), including thionamide derivatives of thiouracyil (PTU), i.e. propylthiouracil and imidazole-thiamazole, are followed by agranulocytosis, hepatitis, or vasculitis and lupus-like syndrome [85–87], then RIT is necessary. The authors believe that, as with AIT, the application of RIT to individual therapy in GM may be a useful addition to other therapies. This therapy, in particular, can play a very important role in the case of GM relapse. There is no current evidence, only for Wistar rats [88] and mice [89], but this is a combination of genNIS genetics and RIT. However, the authors believe it will be a completely different perspective for non-GM therapy (such as AIT) or in the use of other therapies.

A new hope of RIT therapy using NIS with or without the gene other than in glioblastoma multiforme

Attempts to use the anti-cancer effect of radioactive iodine by means of gene therapy using the sodium-iodine symporter are including more and more cancers, even for organs in which the NIS protein is not physiologically detected. This increases the scientific importance and, above all, the potential clinical use of the symporter in the future. Human cancer cell lines transfected with the NIS gene that have been successfully treated with radioactive iodine in animal models include the following: prostate cancer cells [57, 58, 90], multiple myeloma [55], non-small cell lung cancer, neuroendocrine tumours [91], malignant melanoma [58], adenocarcinoma of the breast and ovary [89], cervical cancer [92], renal cancer, GBM [58, 90], and primary liver cancer [88]. There is a dual advantage to performing NIS gene transfer: it is therapeutic, and it enables imaging of transgenic protein expression. The evaluation of transgenic protein expression requires an inva-

sive biopsy or even the death of the animal subjected to gene therapy [93]. Meanwhile, the use of NIS gene transfer may enable non-invasive and reproducible visualisation of vector expression, which may be an important tool in preclinical and clinical gene therapy trials [54]. The use of the NIS gene as an imaging reporter gene (Imagene) allows the assessment of the location and the concentration and duration of expression of the transgenic protein.

NIS, which is found in extrathyroid tissues, does not differ in primary structure — the cDNA of the NIS protein found in the parotid gland, mammary gland, and gastric mucosa has the same nucleotide sequence as the symporter gene found in the thyroid gland [8].

Gene therapy with the use of the NIS gene, however, requires the resolution of several issues, such as whether post-translational processes, including the distribution of the NIS protein to the cell membrane, affect iodine uptake in cells expressing the exogenous symporter [54]. As many studies have shown, the cellular distribution of the symporter is a disorder-prone process and may, therefore, be a limiting factor for iodine uptake by the exogenous NIS protein. This highlights the role of RIT in a highly significant way, and we must especially consider patients with hyperthyroidism. However, in our opinion, it is worth trying RIT even in patients with euthyroidism [81, 84]. But what do we have to lose with a very heavy GM therapy?

REVIEW

Discussion

Is it worth delivering the NIS gene to non-thyroid tumours? Kitzberger et al. [50] introduced an essential, future-proof therapy in the clinical translation of NIS gene therapy (non-virology) for extrathyroidal tumours. This therapy is an effective and safe development of gene delivery vehicles that enable sufficient and tumour-selective NIS expression levels. These authors have additionally proven that this occurs best when there is systemic application of the vector. In addition to options for monitoring and targeting primary tumours, some of these approaches provide metastasis treatment options by enhanced targeted NIS transgene delivery. Synthetic polyplexes and mesenchymal stem cells can deliver anti-cancer therapies after systemic administration through different targeting strategies. Both systems are promising platforms with the potential for clinical success [49]. As previously shown, NIS has also been demonstrated in other organs [8, 17, 94–101].

The sodium-iodine symporter, which is found in extrathyroid tissues, does not differ in primary structure — the cDNA of the NIS protein found in the parotid gland, mammary gland, and gastric mucosa has the same nucleotide sequence as the symporter gene located in the thyroid gland [8]. In extrathyroid tissues, expression of the NIS protein is regulated differently and is generally weaker than in the thyroid gland [49]. Therefore, the question should be asked whether it is worth treating these other tumours (and not just thyroid glands) with RIT alone, but in significantly increased doses. And what is the risk, since GM patients live very short lives, and could this be a "revolution"? The only "complication" is hypothyroidism. Or maybe it is worth trying, especially since the patient does not have anything to risk anymore. The still unresolved question is whether the use of RIT also fulfils its role in the treatment of breast cancer, lung cancer, or glioblastoma multiforme. Although, we have not studied the expression of this protein, and there is still no conclusive evidence for the effect of RIT therapy alone in the case of recurrent glioblastoma, maybe it is worth the risk. Because the most important thing is that life is worth living, and can RIT help this, and perhaps contribute to healing?

Authors' contributions

Conception: A.Cz. Design: A.Cz., P.G., M.B., M.R. and A.F. Writing manuscript: A.Cz., M.B., P.C., N.S.G., B.K.-K. Writing — review and editing: A.Cz., P.G., M.B., P.C., N.S.G., B.K.-K., A.F. The manuscript was drafted by A.Cz., P.G., B.K.-K., M.R., and A.F. and edited by all authors. All authors have carefully read and improved the manuscript.

Conflict of interest

The authors have no conflicts of interest to declare.

Funding

This manuscript has received no funding.

References

1. Luster M, Pfestroff A, Hänscheid H, et al. Radioiodine Therapy. Semin Nucl Med. 2017; 47(2): 126–134, doi: 10.1053/j.semnuclmed.2016.10.002, indexed in Pubmed: 28237001.
2. Levy O, Dai G, Riedel C, et al. Cloning and characterization of the thyroid iodide transporter. Nature. 1996; 379(6564): 458–460, doi: 10.1038/379458a0, indexed in Pubmed: 8559252.
3. Spitzweg C, Joba W, Eisenmenger W, et al. Analysis of human sodium iodide symporter gene expression in extrathyroidal tissues and cloning of its complementary deoxyribonucleic acids from salivary gland, mammary gland, and gastric mucosa. J Clin Endocrinol Metab. 1998; 83(5): 1746–1751, doi: 10.1210/jcem.83.5.4839, indexed in Pubmed: 9589686.
4. Carrasco N. Thyroid iodide transport: the Na+ /J – symporter (NIS). In: Braveman LE, Utiger RD. ed. Werner & Ingbar's the thyroid: a fundamental and clinical text. Lippincott Wiliams & Wilkins, Philadelphia 2000: Philadelphia.
5. De La Vieja A, Dohan O, Levy O, et al. Molecular analysis of the sodium/iodide symporter: impact on thyroid and extrathyroid pathophysiology. Physiol Rev. 2000; 80(3): 1083–1105, doi: 10.1152/physrev.2000.80.3.1083, indexed in Pubmed: 10893432.
6. Hingorani M, Spitzweg C, Vassaux G, et al. The biology of the sodium iodide symporter and its potential for targeted gene delivery. Curr Cancer Drug Targets. 2010; 10(2): 242–267, doi: 10.2174/156800910791054194, indexed in Pubmed: 20201784.
7. Llorente-Esteban A, Manville RW, Reyna-Neyra A, et al. Allosteric regulation of mammalian Na/I symporter activity by perchlorate. Nat Struct Mol Biol. 2020; 27(6): 533–539, doi: 10.1038/s41594-020-0417-5, indexed in Pubmed: 32451489.
8. Spitzweg C, Bible KC, Hofbauer LC, et al. Advanced radioiodine-refractory differentiated thyroid cancer: the sodium iodide symporter

and other emerging therapeutic targets. Lancet Diabetes Endocrinol. 2014; 2(10): 830–842, doi: 10.1016/S2213-8587(14)70051-8, indexed in Pubmed: 24898835.
9. Spitzweg C, Nelson PJ, Wagner E, et al. The sodium iodide symporter (NIS): novel applications for radionuclide imaging and treatment. Endocr Relat Cancer. 2021; 28(10): T193–T213, doi: 10.1530/ERC-21-0177, indexed in Pubmed: 34259647.
10. Willhauck MJ, Sharif Samani BR, Gildehaus FJ, et al. Application of 188rhenium as an alternative radionuclide for treatment of prostate cancer after tumor-specific sodium iodide symporter gene expression. J Clin Endocrinol Metab. 2007; 92(11): 4451–4458, doi: 10.1210/jc.2007-0402, indexed in Pubmed: 17698909.
11. Willhauck MJ, Samani BRS, Wolf I, et al. The potential of 211Astatine for NIS-mediated radionuclide therapy in prostate cancer. Eur J Nucl Med Mol Imaging. 2008; 35(7): 1272–1281, doi: 10.1007/s00259-008-0775-4, indexed in Pubmed: 18404268.
12. Dadachova E, Bouzahzah B, Zuckier LS, et al. Rhenium-188 as an alternative to Iodine-131 for treatment of breast tumors expressing the sodium/iodide symporter (NIS). Nucl Med Biol. 2002; 29(1): 13–18, doi: 10.1016/s0969-8051(01)00279-7, indexed in Pubmed: 11786271.
13. Shimura H, Haraguchi K, Miyazaki A, et al. Iodide uptake and experimental 131I therapy in transplanted undifferentiated thyroid cancer cells expressing the Na+/I- symporter gene. Endocrinology. 1997; 138(10): 4493–4496, doi: 10.1210/endo.138.10.5571, indexed in Pubmed: 9322970.
14. Levy O, Vieja AD, Ginter C, et al. N-linked Glycosylation of the Thyroid Na+/I− Symporter (NIS). J Biol Chem. 1998; 273(35): 22657–22663, doi: 10.1074/jbc.273.35.22657, indexed in Pubmed: 9712895.
15. Mian C, Lacroix L, Alzieu L, et al. Sodium iodide symporter and pendrin expression in human thyroid tissues. Thyroid. 2001; 11(9): 825–830, doi: 10.1089/105072501316973073, indexed in Pubmed: 11575851.
16. Jhiang SM, Cho JY, Ryu KY, et al. An immunohistochemical study of Na+/I- symporter in human thyroid tissues and salivary gland tissues. Endocrinology. 1998; 139(10): 4416–4419, doi: 10.1210/endo.139.10.6329, indexed in Pubmed: 9751526.
17. Wapnir IL, van de Rijn M, Nowels K, et al. Immunohistochemical profile of the sodium/iodide symporter in thyroid, breast, and other carcinomas using high density tissue microarrays and conventional sections. J Clin Endocrinol Metab. 2003; 88(4): 1880–1888, doi: 10.1210/jc.2002-021544, indexed in Pubmed: 12679487.
18. Joba W, Spitzweg C, Schriever K, et al. Analysis of human sodium/iodide symporter, thyroid transcription factor-1, and paired-box-protein-8 gene expression in benign thyroid diseases. Thyroid. 1999; 9(5): 455–466, doi: 10.1089/thy.1999.9.455, indexed in Pubmed: 10365677.
19. Kogai T, Endo T, Saito T, et al. Regulation by thyroid-stimulating hormone of sodium/iodide symporter gene expression and protein levels in FRTL-5 cells. Endocrinology. 1997; 138(6): 2227–2232, doi: 10.1210/endo.138.6.5189, indexed in Pubmed: 9165005.
20. Venkataraman GM, Yatin M, Ain KB. Cloning of the human sodium-iodide symporter promoter and characterization in a differentiated human thyroid cell line, KAT-50. Thyroid. 1998; 8(1): 63–69, doi: 10.1089/thy.1998.8.63, indexed in Pubmed: 9492156.
21. Smyth P, Dwyer RM. The sodium iodide symporter and thyroid disease. Commentary. Clin Endocrinol 2002; 56:427–429. .109/thy.199. Clin Endocrinol. 2002; 56(4): 427–429, doi: 10.1089/thy.1998.8.63, indexed in Pubmed: 11966734.
22. Riedel C, Levy O, Carrasco N. Post-transcriptional regulation of the sodium/iodide symporter by thyrotropin. J Biol Chem. 2001; 276(24): 21458–21463, doi: 10.1074/jbc.M100561200, indexed in Pubmed: 11290744.
23. Chung JK. Sodium iodide symporter: its role in nuclear medicine. J Nucl Med. 2002; 43(9): 1188–1200, indexed in Pubmed: 12215558.
24. Uyttersprot N, Pelgrims N, Carrasco N, et al. Moderate doses of iodide in vivo inhibit cell proliferation and the expression of thyroperoxidase and Na+/I- symporter mRNAs in dog thyroid. Mol Cell Endocrinol. 1997; 131(2): 195–203, doi: 10.1016/s0303-7207(97)00108-1, indexed in Pubmed: 9296378.
25. Eng PH, Cardona GR, Previti MC, et al. Regulation of the sodium iodide symporter by iodide in FRTL-5 cells. Eur J Endocrinol. 2001; 144(2): 139–144, doi: 10.1530/eje.0.1440139, indexed in Pubmed: 11182750.
26. Scipioni A, Ferretti E, Soda G, et al. hNIS protein in thyroid: the iodine supply influences its expression and localization. Thyroid. 2007; 17(7): 613–618, doi: 10.1089/thy.2007.0064, indexed in Pubmed: 17696829.
27. Kohn LD, Suzuki K, Nakazato M, et al. Effects of thyroglobulin and pendrin on iodide flux through the thyrocyte. Trends Endocrinol Metab. 2001; 12(1): 10–16, doi: 10.1016/s1043-2760(00)00337-4, indexed in Pubmed: 11137035.
28. Suzuki K, Mori A, Saito J, et al. Follicular thyroglobulin suppresses iodide uptake by suppressing expression of the sodium/iodide symporter gene. Endocrinology. 1999; 140(11): 5422–5430, doi: 10.1210/endo.140.11.7124, indexed in Pubmed: 10537174.
29. Wolff J, Chaikoff IL. Plasma inorganic iodide as a homeostatic regulator of thyroid function. J Biol Chem. 1948; 174(2): 555–564, indexed in Pubmed: 18865621.
30. Wolff J, Chaikoff IL. The temporary nature of the inhibitory action of excess iodine on organic iodine synthesis in the normal thyroid. Endocrinology. 1949; 45(5): 504–13, illust, doi: 10.1210/endo-45-5-504, indexed in Pubmed: 15396709.
31. Spitzweg C, Joba W, Morris JC, et al. Regulation of sodium iodide symporter gene expression in FRTL-5 rat thyroid cells. Thyroid. 1999; 9(8): 821–830, doi: 10.1089/thy.1999.9.821, indexed in Pubmed: 10482376.
32. Eng PH, Cardona GR, Fang SL, et al. Escape from the acute Wolff-Chaikoff effect is associated with a decrease in thyroid sodium/iodide symporter messenger ribonucleic acid and protein. Endocrinology. 1999; 140(8): 3404–3410, doi: 10.1210/endo.140.8.6893, indexed in Pubmed: 10433193.
33. Spitzweg C, Morris JC. The sodium iodide symporter: its pathophysiological and therapeutic implications. Clin Endocrinol (Oxf). 2002; 57(5): 559–574, doi: 10.1046/j.1365-2265.2002.01640.x, indexed in Pubmed: 12390328.
34. Ajjan RA, Kamaruddin NA, Crisp M, et al. Regulation and tissue distribution of the human sodium iodide symporter gene. Clin Endocrinol (Oxf). 1998; 49(4): 517–523, doi: 10.1046/j.1365-2265.1998.00570.x, indexed in Pubmed: 9876351.
35. Ajjan RA, Watson PF, Findlay C, et al. The sodium iodide symporter gene and its regulation by cytokines found in autoimmunity. J Endocrinol. 1998; 158(3): 351–358, doi: 10.1677/joe.0.1580351, indexed in Pubmed: 9846164.
36. Morshed SA, Davies TF. Graves' Disease Mechanisms: The Role of Stimulating, Blocking, and Cleavage Region TSH Receptor Antibodies. Horm Metab Res. 2015; 47(10): 727–734, doi: 10.1055/s-0035-1559633, indexed in Pubmed: 26361259.
37. Ajjan RA, Findlay C, Metcalfe RA, et al. The modulation of the human sodium iodide symporter activity by Graves' disease sera. J Clin Endocrinol Metab. 1998; 83(4): 1217–1221, doi: 10.1210/jcem.83.4.4701, indexed in Pubmed: 9543144.
38. Tuttle R, Patience T, Budd S. Treatment with Propylthiouracil before Radioactive Iodine Therapy Is Associated with a Higher Treatment Failure Rate Than Therapy with Radioactive Iodine Alone in Graves' Disease. Thyroid. 1995; 5(4): 243–247, doi: 10.1089/thy.1995.5.243.
39. Sabri O, Zimny M, Schreckenberger M, et al. Success rate of radioiodine therapy in Graves' disease: the influence of thyrostatic medication. J Clin Endocrinol Metab. 1999; 84(4): 1229–1233, doi: 10.1210/jcem.84.4.5588, indexed in Pubmed: 10199759.
40. Sabri O, Zimny M, Schulz G, et al. Success rate of radioiodine therapy in Graves' disease: the influence of thyrostatic medication. J Clin Endocrinol Metab. 1999; 84(4): 1229–1233, doi: 10.1210/jcem.84.4.5588, indexed in Pubmed: 10199759.
41. Furlanetto TW, Nunes RB, Sopelsa AM, et al. Estradiol decreases iodide uptake by rat thyroid follicular FRTL-5 cells. Braz J Med Biol Res. 2001; 34(2): 259–263, doi: 10.1590/s0100-879x2001000200015, indexed in Pubmed: 11175503.
42. Pekary AE, Hershman JM. Tumor necrosis factor, ceramide, transforming growth factor-beta1, and aging reduce Na+/I- symporter messenger ribonucleic acid levels in FRTL-5 cells. Endocrinology. 1998; 139(2): 703–712, doi: 10.1210/endo.139.2.5760, indexed in Pubmed: 9449644.
43. Louis DN, Perry A, Wesseling P, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. 2016; 131(6): 803–820, doi: 10.1007/s00401-016-1545-1, indexed in Pubmed: 27157931.
44. Guo R, Xi Y, Zhang M, et al. Human sodium iodide transporter gene-mediated imaging and therapy of mouse glioma, comparison between Re and I. Oncol Lett. 2018; 15(3): 3911–3917, doi: 10.3892/ol.2018.7752, indexed in Pubmed: 29467904.
45. Cho JY, Shen DHY, Yang W, et al. In vivo imaging and radioiodine therapy following sodium iodide symporter gene transfer in animal model of intracerebral gliomas. Gene Ther. 2002; 9(17): 1139–1145, doi: 10.1038/sj.gt.3301787, indexed in Pubmed: 12170377.
46. Opyrchal M, Allen C, Msaouel P, et al. Effective radiovirotherapy for malignant gliomas by using oncolytic measles virus strains encoding the sodium iodide symporter (MV-NIS). Hum Gene Ther. 2012; 23(4): 419–427, doi: 10.1089/hum.2011.158, indexed in Pubmed: 22185260.
47. Ravera S, Reyna-Neyra A, Ferrandino G, et al. The Sodium/Iodide Symporter (NIS): Molecular Physiology and Preclinical and Clinical Applications. Annu Rev Physiol. 2017; 79: 261–289, doi: 10.1146/annurev-physiol-022516-034125, indexed in Pubmed: 28192058.
48. Jiang H, Bansal A, Pandey MK, et al. Synthesis of 18F-Tetrafluoroborate via Radiofluorination of Boron Trifluoride and Evaluation in a Murine C6-Glioma Tumor Model. J Nucl Med. 2016; 57(9): 1454–1459, doi: 10.2967/jnumed.115.170894, indexed in Pubmed: 27103021.
49. Kitzberger C, Spellerberg R, Morath V, et al. The sodium iodide symporter (NIS) as theranostic gene: its emerging role in new imaging modalities and non-viral gene therapy. EJNMMI Res. 2022; 12(1): 25, doi: 10.1186/s13550-022-00888-w, indexed in Pubmed: 35503582.
50. Niess H, von Einem JC, Thomas MN, et al. Treatment of advanced gastrointestinal tumors with genetically modified autologous mesenchymal

stromal cells (TREAT-ME1): study protocol of a phase I/II clinical trial. BMC Cancer. 2015; 15: 237, doi: 10.1186/s12885-015-1241-x, indexed in Pubmed: 25879229.
51. Khoshnevisan A, Jauregui-Osoro M, Shaw K, et al. [(18)F]tetrafluoroborate as a PET tracer for the sodium/iodide symporter: the importance of specific activity. EJNMMI Res. 2016; 6(1): 34, doi: 10.1186/s13550-016-0188-5, indexed in Pubmed: 27103614.
52. Portulano C, Paroder-Belenitsky M, Carrasco N. The Na+/I- symporter (NIS): mechanism and medical impact. Endocr Rev. 2014; 35(1): 106–149, doi: 10.1210/er.2012-1036, indexed in Pubmed: 24311738.
53. Spellerberg R, Benli-Hoppe T, Kitzberger C, et al. Selective sodium iodide symporter () genetherapy of glioblastoma mediatedby EGFR-targeted lipopolyplexes. Mol Ther Oncolytics. 2021; 23: 432–446, doi: 10.1016/j.omto.2021.10.011, indexed in Pubmed: 34853814.
54. Vadysirisack DD, Shen DH, Jhiang SM. Correlation of Na+/I- symporter expression and activity: implications of Na+/I- symporter as an imaging reporter gene. J Nucl Med. 2006; 47(1): 182–190, indexed in Pubmed: 16391203.
55. Huang M, Batra RK, Kogai T, et al. Ectopic expression of the thyroperoxidase gene augments radioiodide uptake and retention mediated by the sodium iodide symporter in non-small cell lung cancer. Cancer Gene Ther. 2001; 8(8): 612–618, doi: 10.1038/sj.cgt.7700354, indexed in Pubmed: 11571539.
56. Dingli D, Bergert ER, Bajzer Z, et al. Dynamic iodide trapping by tumor cells expressing the thyroidal sodium iodide symporter. Biochem Biophys Res Commun. 2004; 325(1): 157–166, doi: 10.1016/j.bbrc.2004.09.219, indexed in Pubmed: 15522214.
57. Spitzweg C, Dietz AB, O'Connor MK, et al. In vivo sodium iodide symporter gene therapy of prostate cancer. Gene Ther. 2001; 8(20): 1524–1531, doi: 10.1038/sj.gt.3301558, indexed in Pubmed: 11704812.
58. Elisei R, Vivaldi A, Ciampi R, et al. Treatment with drugs able to reduce iodine efflux significantly increases the intracellular retention time in thyroid cancer cells stably transfected with sodium iodide symporter complementary deoxyribonucleic acid. J Clin Endocrinol Metab. 2006; 91(6): 2389–2395, doi: 10.1210/jc.2005-2480, indexed in Pubmed: 16537683.
59. Amyes EW, Deeb PH, Vogel PJ, et al. Determining the site of brain tumors; the use of radioactive iodine and phosphorus. Calif Med. 1955; 82(3): 167–170, indexed in Pubmed: 14351985.
60. Palande V, Siegal T, Detroja R, et al. Detection of gene mutations and gene-gene fusions in circulating cell-free DNA of glioblastoma patients: an avenue for clinically relevant diagnostic analysis. Mol Oncol. 2022; 16(10): 2098–2114, doi: 10.1002/1878-0261.13157, indexed in Pubmed: 34875133.
61. Gleevec (imatinib mesylate) tablet. Daily Med; U.S. National Library of Medicine.
62. Sun Li, Liang C, Shirazian S, et al. Discovery of 5-[5-fluoro-2-oxo-1,2-dihydroindol-(3Z)-ylidenemethyl]-2,4- dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide, a novel tyrosine kinase inhibitor targeting vascular endothelial and platelet-derived growth factor receptor tyrosine kinase. J Med Chem. 2003; 46(7): 1116–1119, doi: 10.1021/jm0204183, indexed in Pubmed: 12646019.
63. Strumberg D. Preclinical and clinical development of the oral multikinase inhibitor sorafenib in cancer treatment. Drugs Today (Barc). 2005; 41(12): 773–784, doi: 10.1358/dot.2005.41.12.937959, indexed in Pubmed: 16474853.
64. Murphy DA, Makonnen S, Lassoued W, et al. Inhibition of tumor endothelial ERK activation, angiogenesis, and tumor growth by sorafenib (BAY43-9006). Am J Pathol. 2006; 169(5): 1875–1885, doi: 10.2353/ajpath.2006.050711, indexed in Pubmed: 17071608.
65. König D, Hench J, Frank S, et al. Larotrectinib Response in NTRK3 Fusion-Driven Diffuse High-Grade Glioma. Pharmacology. 2022; 107(7-8): 433–438, doi: 10.1159/000524399, indexed in Pubmed: 35526519.
66. Subbiah V, Velcheti V, Tuch BB, et al. Selective RET kinase inhibition for patients with RET-altered cancers. Ann Oncol. 2018; 29(8): 1869–1876, doi: 10.1093/annonc/mdy137, indexed in Pubmed: 29912274.
67. https://www.magforce.com/news/?article=375.
68. Schirrmacher V. Cancer Vaccines and Oncolytic Viruses Exert Profoundly Lower Side Effects in Cancer Patients than Other Systemic Therapies: A Comparative Analysis. Biomedicines. 2020; 8(3), doi: 10.3390/biomedicines8030061, indexed in Pubmed: 32188078.
69. Schirrmacher V, Lorenzen D, Van Go, et al. A new strategy of cancer immunotherapy combining hyperthermia/oncolytic virus pretreatment with specific autologous anti-tumor vaccination — A Review. Austin Oncol Case Rep. 2017; 2: 1006, doi: 10.26420/austinoncolcaserep.1006.2017.
70. Lowenfeld L, Mick R, Datta J, et al. Dendritic Cell Vaccination Enhances Immune Responses and Induces Regression of HER2 DCIS Independent of Route: Results of Randomized Selection Design Trial. Clin Cancer Res. 2017; 23(12): 2961–2971, doi: 10.1158/1078-0432.CCR-16-1924, indexed in Pubmed: 27965306.
71. Obara W, Kanehira M, Katagiri T, et al. Present status and future perspective of peptide-based vaccine therapy for urological cancer. Cancer Sci. 2018; 109(3): 550–559, doi: 10.1111/cas.13506, indexed in Pubmed: 29345737.
72. Chamani R, Ranji P, Hadji M, et al. Application of E75 peptide vaccine in breast cancer patients: A systematic review and meta-analysis. Eur J Pharmacol. 2018; 831: 87–93, doi: 10.1016/j.ejphar.2018.05.010, indexed in Pubmed: 29753042.
73. Hilf N, Kuttruff-Coqui S, Frenzel K, et al. Actively personalized vaccination trial for newly diagnosed glioblastoma. Nature. 2019; 565(7738): 240–245, doi: 10.1038/s41586-018-0810-y, indexed in Pubmed: 30568303.
74. Schirrmacher V, van Gool S, Stuecker W. Breaking Therapy Resistance: An Update on Oncolytic Newcastle Disease Virus for Improvements of Cancer Therapy. Biomedicines. 2019; 7(3), doi: 10.3390/biomedicines7030066, indexed in Pubmed: 31480379.
75. Artusio E, Hathaway B, Stanson J, et al. Transfection of human monocyte-derived dendritic cells with native tumor DNA induces antigen-specific T-cell responses in vitro. Cancer Biol Ther. 2006; 5(12): 1624–1631, doi: 10.4161/cbt.5.12.3353, indexed in Pubmed: 17172816.
76. Anguille S, Van de Velde AL, Smits EL, et al. Dendritic cell vaccination as postremission treatment to prevent or delay relapse in acute myeloid leukemia. Blood. 2017; 130(15): 1713–1721, doi: 10.1182/blood-2017-04-780155, indexed in Pubmed: 28830889.
77. Wang B, He J, Liu C, et al. An effective cancer vaccine modality: lentiviral modification of dendritic cells expressing multiple cancer-specific antigens. Vaccine. 2006; 24(17): 3477–3489, doi: 10.1016/j.vaccine.2006.02.025, indexed in Pubmed: 16530303.
78. Van Gool SW, Makalowski J, Feyen O, et al. The induction of immunogenic cell death (ICD) during maintenance chemotherapy and subsequent multimudal immunotherapy for glioblastoma (GBM). Austin Oncol Case Rep. 2018; 3: 1010.
79. Gubin MM, Artyomov MN, Mardis ER, et al. Tumor neoantigens: building a framework for personalized cancer immunotherapy. J Clin Invest. 2015; 125(9): 3413–3421, doi: 10.1172/JCI80008, indexed in Pubmed: 26258412.
80. Schirrmacher V. Oncolytic Newcastle disease virus as a prospective anti-cancer therapy. A biologic agent with potential to break therapy resistance. Expert Opin Biol Ther. 2015; 15(12): 1757–1771, doi: 10.1517/14712598.2015.1088000, indexed in Pubmed: 26436571.
81. Czarnywojtek A, Warmuz-Stangierska I, Woliński K, et al. Radioiodine therapy in patients with type II amiodarone-induced thyrotoxicosis. Pol Arch Med Wewn. 2014; 124(12): 695–703, doi: 10.20452/pamw.2556, indexed in Pubmed: 25394637.
82. Hermida J. Radioiodine ablation of the thyroid to prevent recurrence of amiodarone-induced thyrotoxicosis in patients with resistant tachyarrhythmias. Europace. 2004; 6(2): 169–174, doi: 10.1016/j.eupc.2003.11.002, indexed in Pubmed: 15018878.
83. Gursoy A, Tutuncu NB, Gencoglu A, et al. Radioactive iodine in the treatment of type-2 amiodarone-induced thyrotoxicosis. J Natl Med Assoc. 2008; 100(6): 716–719, doi: 10.1016/s0027-9684(15)31348-1, indexed in Pubmed: 18595575.
84. Czarnywojtek A, Zgorzalewicz-Stachowiak M, Woliński K, et al. Results of preventive radioiodine therapy in euthyroid patients with history of hyperthyroidism prior to administration of amiodarone with permanent atrial fibrillation--a preliminary study. Endokrynol Pol. 2014; 65(4): 269–274, doi: 10.5603/EP.2014.0036, indexed in Pubmed: 25185848.
85. Joseph F, Younis N, Bowen-Jones D. Treatment of carbimazole-induced agranulocytosis and sepsis with granulocyte colony stimulating factor. International Journal of Clinical Practice. 2003; 57(2): 145–146, doi: 10.1111/j.1742-1241.2003.tb10445.x.
86. Wiersinga WM. Amiodarone and the thyroid. In: Weetman AP, Grossman A. ed. Pharmacoterapeutics of the thyroid gland. Springer Verlag, Berlin 1997.
87. Otsuka F, Noh JY, Chino T, et al. Hepatotoxicity and cutaneous reactions after antithyroid drug administration. Clin Endocrinol (Oxf). 2012; 77(2): 310–315, doi: 10.1111/j.1365-2265.2012.04365.x, indexed in Pubmed: 22332800.
88. Faivre J, Clerc J, Gérolami R, et al. Long-term radioiodine retention and regression of liver cancer after sodium iodide symporter gene transfer in wistar rats. Cancer Res. 2004; 64(21): 8045–8051, doi: 10.1158/0008-5472.CAN-04-0893, indexed in Pubmed: 15520214.
89. Dwyer RM, Bergert ER, O'Connor MK, et al. Sodium iodide symporter-mediated radioiodide imaging and therapy of ovarian tumor xenografts in mice. Gene Ther. 2006; 13(1): 60–66, doi: 10.1038/sj.gt.3302599, indexed in Pubmed: 16121204.
90. Mitrofanova E, Unfer R, Vahanian N, et al. Rat sodium iodide symporter for radioiodide therapy of cancer. Clin Cancer Res. 2004; 10(20): 6969–6976, doi: 10.1158/1078-0432.CCR-04-0687, indexed in Pubmed: 15501976.
91. Schipper ML, Weber A, Behe M, et al. Radioiodine treatment after sodium iodide symporter gene transfer is a highly effective therapy in neuroendocrine tumor cells. Cancer Res. 2003; 63(3): 1333–1338, indexed in Pubmed: 12649195.
92. Boland A, Ricard M, Opolon P, et al. Adenovirus-mediated transfer of the thyroid sodium/iodide symporter gene into tumors for a targeted radiotherapy. Cancer Res. 2000; 60(13): 3484–3492, indexed in Pubmed: 10910060.

93. Wolny M, Syrenicz A. [Sodium iodide symporter in physiology and diseases -- the current state of knowledge]. Endokrynol Pol. 2007; 58(6): 512–521, indexed in Pubmed: 18205108.
94. Spitzweg C, Joba W, Schriever K, et al. Analysis of human sodium iodide symporter immunoreactivity in human exocrine glands. J Clin Endocrinol Metab. 1999; 84(11): 4178–4184, doi: 10.1210/jcem.84.11.6117, indexed in Pubmed: 10566669.
95. Cho JY. Hormonal Regulation of Radioiodide Uptake Activity and Na+/I- Symporter Expression in Mammary Glands. J Clin Endocrinol Metab. 2000; 85(8): 2936–2943, doi: 10.1210/jc.85.8.2936, indexed in Pubmed: 10946907.
96. Bruno R, Giannasio P, Ronga G, et al. Sodium iodide symporter expression and radioiodine distribution in extrathyroidal tissues. J Endocrinol Invest. 2004; 27(11): 1010–1014, doi: 10.1007/BF03345302, indexed in Pubmed: 15754731.
97. Morgenstern KE, Vadysirisack DD, Zhang Z, et al. Expression of sodium iodide symporter in the lacrimal drainage system: implication for the mechanism underlying nasolacrimal duct obstruction in I(131)-treated patients. Ophthalmic Plast Reconstr Surg. 2005; 21(5): 337–344, doi: 10.1097/01.iop.0000179369.75569.a8, indexed in Pubmed: 16234694.
98. Tazebay UH, Wapnir IL, Levy O, et al. The mammary gland iodide transporter is expressed during lactation and in breast cancer. Nat Med. 2000; 6(8): 871–878, doi: 10.1038/78630, indexed in Pubmed: 10932223.
99. Upadhyay G, Singh R, Agarwal G, et al. Functional expression of sodium iodide symporter (NIS) in human breast cancer tissue. Breast Cancer Res Treat. 2003; 77(2): 157–165, doi: 10.1023/a:1021321409159, indexed in Pubmed: 12602914.
100. Smanik PA, Ryu KY, Theil KS, et al. Expression, exon-intron organization, and chromosome mapping of the human sodium iodide symporter. Endocrinology. 1997; 138(8): 3555–3558, doi: 10.1210/endo.138.8.5262, indexed in Pubmed: 9231811.
101. Spitzweg C, Scholz IV, Bergert ER, et al. Retinoic acid-induced stimulation of sodium iodide symporter expression and cytotoxicity of radioiodine in prostate cancer cells. Endocrinology. 2003; 144(8): 3423–3432, doi: 10.1210/en.2002-0206, indexed in Pubmed: 12865321.