

A Comprehensive Look on Conjugated Targeted Therapies as A Novel Candidate for Personalized Thyroid Carcinoma Treatment

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Abstract:

Thyroid cancer is a substantial threat worldwide due to its prevalence and complication it follows. Current therapy is widely available, although failed to address the burdens associated with the disease, thus requiring a newer approach. Recently, the novel discovery of conjugated targeted therapy and its potential implementation enables a more specific, cancer-targeting mechanism, with potentially higher efficacy and minimum adverse effect than conventional treatments. This review was made to assess its potential, via comprehensive screening on several databases, such as Cochrane, PubMed, Scopus,

ScienceDirect, and Wiley with set criterions. The search yielded 6 viable studies analyzing different forms of targeted therapies. Based on the included studies, conjugated targeted therapy displayed high selectivity and cytotoxicity toward cancer cells, while remained tolerable toward normal cells and the host. Not only as a therapeutic agent, this therapy also possessed imaging enhancement and metastasis detection, indicating high diagnostic value. Although, applicability and cost- efficiency of the treatment should be considered, due to extra costs in biosynthesizing therapeutic agents and phenotyping of targeted cells. Nonetheless, the high selectivity and potentially better safety profile of conjugated targeted therapy should be assessed further, and weighed with its limitations. All in all, conjugated targeted therapy has been proven to be selective towards cancer cell and a potent candidate as personalized treatment. Biosafety analysis of its implementation is recommended, followed by further clinical trials on human samples.

Keywords: antibody drug conjugate, carcinoma, targeted therapy, thyroid neoplasms

Introduction:

Thyroid cancer has been an increasing cause of concern worldwide, ranked as the 9th most common cancer with the greatest trend of increase in men and regions with middle socio-demographic index (SDI).¹ In 2016, the number of thyroid cases worldwide is 238,000, and within only 2 years, the incidence has increased by 1.28 to 567,000 cases in 2018. Aside from causing significant morbidity and mortality, thyroid cancer also disrupts the balance of hormones, since thyroid is involved in many bodily functions. Currently, the standard treatment for thyroid cancer involves surgery and later radioactive iodine therapy or thyroid stimulating hormone (TSH) suppression. However, medullary and anaplastic thyroid cancer are more difficult to treat and thus as of now proposed treatments have only reached the phase of clinical trials, without significant established benefits when used singularly. While resection has insufficient benefits in treating metastatic thyroid cancer, iodine therapy carries the risk of second cancer, suppression of TSH the risk for hormonal disbalances, and drug combinations the risk of severe adverse effects without any clinically significant advantages.¹ In the face of COVID-19, diagnosis, monitoring, and management of thyroid cancer has become even

more challenging since availability of intensive care units, nuclear medicine services, and operating theaters have been limited, monitoring has been restricted, and there has to be consideration against risk of COVID-19 exposure in medical settings.² Moreover, recent data has shown that malignancy significantly causes elevated risk of ICU admission and mortality (HR:3.50[95%CI:1.60-7.64]).³ Thus, it is of paramount importance that a more effective and efficient targeted treatment modality is developed, which allows better management and therefore reduced mortality due to thyroid cancer without causing extensive side effects.

There are various recent advancements that have pointed out potential drug targets, including the discovery of folate receptor expression in thyroid cancer cells, allowing the innovation of folate-mediated drug delivery,⁴ the production of carcinoembryonic antigen (CEA) by medullary carcinoma,⁵ which serves as potential targets for antibodies when conjugated with radiotherapy, and nanoparticles that enable better delivery of chemotherapeutic drugs such as methotrexate and fingolimod as well as the use in combination with cetuximab for theragnostic.⁶ Drug conjugation has

the potential to improve targeted delivery hence reducing side effects, hence better effectiveness in treating thyroid cancer. Thus, this literature aims to discuss potential efficacy and the clinical implications of conjugated targeted drug therapies for thyroid carcinoma.

Methods:

This literature review is conducted by the three reviewers screening databases including Cochrane, PubMed, Scopus, ScienceDirect, and Wiley, searching for primary studies and reviews with the inclusion criteria (1) searches for studies implementing drug conjugates as targeted therapy, (2) conducted for any types of thyroid cancer, and (3) study design either preclinical or clinical. Exclusion criteria include (1) studies with irretrievable full-text and (2) studies in languages other than English or Indonesian. Studies screened are within 10 years of publication and we used combination of keywords such as: (drug conjugate OR antibody-drug conjugate OR ADC OR radio-immunotherapy OR Immunotoxins) AND (((("Thyroid Neoplasms"[Mesh]) OR "Thyroid Carcinoma, Anaplastic"[Mesh]) OR "Thyroid Cancer, Papillary"[Mesh])). Further adjustments are made based on each database.

Results and Discussion:

Thyroid Carcinoma and The Endocrine System

Thyroid cancer can come in various clinical presentations ranging from low-risk nodules to high-risk metastatic malignancies. Thyroid nodules, although 90% of which are non-palpable, benign, and clinically insignificant, can in some cases become malignant and cause significant morbidity. Meanwhile, follicular thyroid carcinoma can be differentiated, which is the most common type and comprises 95% of all cases, or anaplastic, which is rare but very aggressive and can coexist with the differentiated type. Neuroendocrine thyroid cancer, which is derived from parafollicular c-cells, is also called medullary thyroid cancer. Commonly presenting as a solitary nodule accompanied by neck lymphadenopathy, this cancer also metastasizes quickly in 70% of patients.¹⁻⁵

Although in early stages minimal symptoms can be identified, as it progresses, thyroid cancer can cause voice hoarseness, dysphagia, and swollen lymph nodes. More importantly, thyroid cancer can cause imbalance of hormones, in the form of hypothyroidism or

hyperthyroidism, which are particularly harmful since thyroid is involved in gene expressions as well as the normal development and functions of the body.⁷ Hypothyroidism can cause fatigue, weight gain, emotional and sleep disturbances, peripheral neuropathy, infertility, as well as the risk of congenital defects for children from mothers with thyroid disturbances. Meanwhile, hyperthyroidism can result in weight loss, disruptions to the digestive system, arrhythmias and heart problems, osteoporosis, and thyroid toxicity. This further prompts the urgency of effective treatment for thyroid cancer.

Current Treatments for Thyroid Carcinoma and Their Pitfalls

The treatment approaches for thyroid cancer are diverse since there has to be a balance between not over-treating benign nodules and the need for aggressive approach in high-risk or advanced diseases. For small, unifocal tumors less than 4 cm without any evidence of spread, lobectomy is the treatment of choice. However, if nodal disease is discovered, total thyroidectomy is required, and in such cases the patient has to undergo lifelong hormone replacement therapy. These procedures should be followed by assessment whether the patient

needs radioiodine ablation, in order to eliminate potential residues of neoplastic foci, or suppression of thyroid stimulating hormone (TSH), in order to reduce recurrence since TSH causes proliferation of both thyrocytes and malignant cells. However, radioiodine therapy carries with it the risk of short-term adverse effects as well as higher chances of relapses or second cancers, and studies have found many patients are unresponsive to this therapy. Moreover, TSH suppression has not yet any clear guidelines for concentrations, and hyperthyroidism that is induced can affect the heart, causing risk of atrial fibrillation for instance, and bones, resulting in osteoporosis.

In recent years, systemic medications have been developed for advanced differentiated and medullary thyroid cancer, including kinase inhibitors such as sorafenib, lenvatinib, vandetanib, and cabozantinib, but these cannot fully cure the disease and some subsets of patients also develop resistance. COVID-19 antiviral drugs also might have potential interactions with systemic thyroid cancer treatments, especially lenvatinib which might increase chances of arrhythmia and cabozantinib which can potentiate drug concentration.² For anaplastic thyroid cancer however, current

interest of exploratory studies have been focused onto BRAF inhibitors, MEK inhibitor, mTOR inhibitors, microtubule inhibitors, PPAR-gamma agonists, and immunotherapy, but considering the rapid progression of the disease, use of one drug alone has not shown any promising results, and drug combinations especially during chemotherapy often result in extensive adverse effects harmful to normal cell functions. Thus, there are various loopholes in current treatment guidelines that can hopefully be solved through the use of drug conjugates, which might provide better drug delivery and improve efficacy while minimizing the occurrence of side effects.

Introduction of Targeted Therapies

Following the limitations brought by current treatments (of cancers in general), targeted agents accompanied by personalized cancer therapy has taken the spotlight for individual treatment of various carcinomas.⁸ Referring back to the advancements made under cancer at a molecular level, specific proteins and cell's DNA pertaining to their involvement in how cancer was able to evade the immune system has been identified. Nicknamed the 'forefront' of cancer treatment, targeted cancer therapies

implement specific pharmacological agents which in turn, inhibits metastases along with promoting apoptosis of individual cancer cells.⁹ Compared to household treatments such as radio- or chemotherapy, targeted therapies zero in on specific proteins involved in tumorigenesis and molecular changes unique to that particular cancer. Hence by doing so, targeted therapies were able to avoid affecting non-neoplastic cells undergoing mitosis (such as bone marrow, hair, and epithelium) and only block specific pathways important for the progression and growth of the particular tumor such as shown in Figure 1.¹⁰

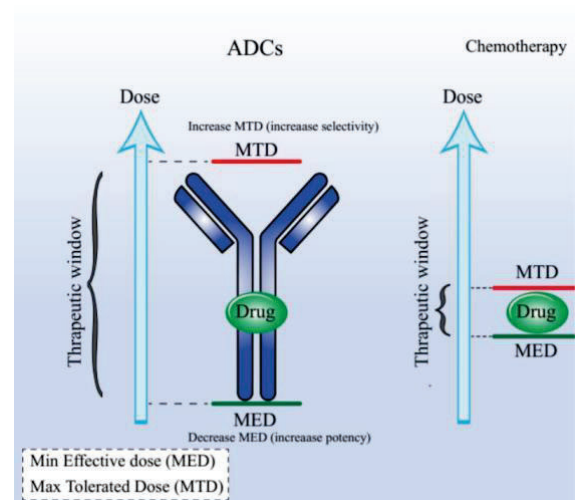


Figure 1. Shows one of the schematic pathways of cell proliferation and tumor progression, potentially blocked by targeted therapy.¹⁰

The specific nature of targeted therapy is considered the biggest selling point in providing more therapeutically beneficial treatment for cancer. Currently there are several acknowledged targeted agents, which include: monoclonal antibodies (mAbs), small molecule inhibitors (SMIs), interfering RNA (iRNA) molecules, and immunotoxins.¹¹ Furthermore, the discovery of antibody-drug-conjugates (ADC) has opened a promising future in conjugated targeted therapies.⁹ By utilizing mAbs and linking them with cytotoxic drugs, ADCs were able to push personalized therapies even further by specifically recognizing antigens expressed by the tumor cells, and deliver their cytotoxic payload without damaging non-neoplastic cells. Moreover, different from normal chemotherapy, ADCs also extend the therapeutic window of drugs via the decrease of minimum effective dose (MTD) and increase of maximum tolerated dose (MTD) (Figure 2). This type of targeted therapy offers advantages compared to the others. Conjugated targeted therapy utilizes targeting molecules, creating a more selective system compared to small molecule inhibitor targeted therapy, which can permeate and possibly interfere with normal cells. The selectivity might widen the therapeutic window of this

therapy and creating less severe adverse effects. This therapy also offer versatility, which can be exploited for various uses, for example as a diagnostic and therapeutic agent. It can also be used for enhancing the efficacy of conventional therapies or as a single regiment drug. Compared to commonly used targeted therapy (SMIs such as tyrosine-kinase inhibitor or TKI), conjugated targeted therapy does not depend on signaling pathway, but rather having the sole purpose of delivering cytotoxic substances, thus making resistance harder to develop. All of these combined advantages make conjugated targeted therapy a prominent candidate for a novel, more effective cancer treatment.¹³

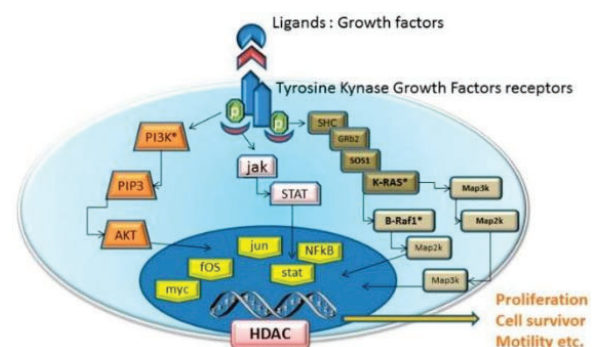


Figure 2. A visual representation on how ADCs were able to increase the therapeutic window of drugs.⁹

Therapeutic Value of Conjugated Targeted Therapy

Based on the qualitative representation of the included studies as shown in Table 1, together with the quantitative measurement provided in the study's respective papers, targeted therapy using conjugated targeting molecules displayed better safety profile and increased cytotoxicity performance than conventional therapy. These discoveries remain consistent across all the included studies, which are ranged from in vitro to clinical trial, further consolidating the therapy projected superiority compared to current regimens and the urgency for further investigation. As a therapeutic agent, conjugated targeted therapy agents differ from each other. The differences lay on the components, which consist of therapeutic agent (drug) and targeting agent (antibody or other targeting components) that can be freely manipulated, enabling tailor-made therapy based on the molecular characteristics of the cancer. The practical example was demonstrated by Jang et al., which agent showed high cytotoxicity toward cancer cells that highly express dysadherin while leaving normal and low-to-moderate-dysadherin-expressing cancer cells unharmed.¹⁸ The selectivity toward a specific type of cell is the main advantage of this technology, which enables minimum collateral damage

that can cause adverse effects and maximum anticancer activity. The aforementioned statement was observed in human by Juweid et al. study which used the older version of targeted therapy.¹⁴⁻¹⁵ Regardless, it showcased tolerable adverse effect, high selectivity (as it was able to detect up to 13 sites of unconfirmed tumor metastases in one patient), and although could not be directly observed, efficacious, indicated by progressive betterment of thyroid biomarkers. Other than selectivity, increased cytotoxicity is also observed, which might be attributable to increased cellular uptake due to its conjugate interactions with tumor cell. Moreover, an in vivo study using chick chorioallantoic membrane also showed anti-metastatic activity of conjugated targeted therapy, though yet to be proven in human or animal model, would be tremendously beneficial for patient with highly metastatic cancer, such as thyroid cancer.^{16,20}

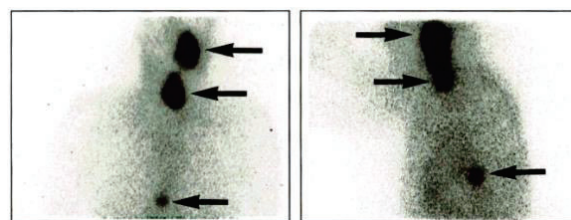


Figure 3. Radioimaging results obtained after 9 days of administration. (Left) Anterior plane and (Right) Lateral Plane of neck and

chest showed lymph node metastasis near the mediastinum (lower arrow)

Conjugated agents also possess high diagnostic value due to their selectivity. Selectivity enables the agent to accumulate in the tumor microenvironment. The accumulation of said agent can be detected using various modalities, such as USG, CT, and MRI scan, thus creating a contrast and easier visualization. As mentioned before, Juweid et al. reported detection of unconfirmed positives of metastatic thyroid cancer, which further solidify the high diagnostic value of conjugated agents. An exemplary radioimaging result can be seen in Fig. 3, showing intense accumulations of agent in tumor sites, which happened to also detects a metastasis in a nearby lymph node.¹⁶⁻¹⁷

There is also a trend of incorporating nanotechnology which enables further control of the treatment. Nanotechnology enables physical intervention, such as local hyperthermia induction. This intratumoral physical intervention is aimed to increase the potency of agent/co-treatment, direct necrosis induction (usually via ablation/direct heat exposure), or for diagnostic purposes. Study by Wang Qimeihui

et al. reported complete removal of engrafted thyroid cancer. They achieved this result using encapsulated infrared dye inside the conjugated nanoparticles, which then irradiated. These procedures induced heat in intratumoral environment which peaked at 57°C, resulting necrosis after 2 days of treatment.¹⁷ Similar approach was adopted by Wang Yang et al. which aimed to release the loaded drug in controlled manner using Low Intensity Frequency Ultrasound (LIFU), yielding increased efficacy and better organ biomarkers profile, indicating good biocompatibility.¹⁴⁻¹⁷ Nanoparticles also function as contrast for various neuroimaging modalities. Both aforementioned studies enhanced USG visualization of the tumor using a phenomenon called microbubble-enhancement, which is created in vivo using perfluoro pentane (PFP), which sublimates at body temperature ($\pm 25^\circ\text{C}$). The resulting PFP vapor then creates mini air pockets called microbubbles. The created microbubbles then resonate in USG field, which is detectable by conventional USG tools.¹⁷⁻²¹

Applicability and Future Prospects

The applicability of conjugated targeted therapies depends on several factors, with some to be

considered being: efficacy, safety profile, cost-effectiveness, and administration process. Based on this review, conjugated targeted therapy presented results as expected by its theoretical hypothesis. Although, realistically, the whole treatment process of using mAbs and other molecular agents are projected to be less cost-efficient than current therapies. A review by Crisci et al. included the outcomes and challenges of implementing wide-scale administration of targeted therapies, with some notable points being: biotechnical costs of producing therapeutics agents, genotyping and phenotyping of tumor tissues, and objectively new competencies needed to be introduced to oncologists worldwide. Nonetheless, the limitations brought by this treatment should be reconsidered rather than avoided. Looking forward, researchers and clinicians are responsible to evaluate the strengths and limitations conjugated targeted therapy has, and integrate those results in formulating a more cost-effective analysis on it. Furthermore, with pharmacogenetic tests being commonly introduced in the development of conjugated targeted therapy, this pioneers the growth of other biomedical technologies such as nano- or immune-diagnostic modalities.¹¹

Strength and Limitations

The strength of this review lies in the strength of the treatment itself. In theory, targeted therapy has been considered to be objectively and therapeutically better for cancer treatment due to its specific mechanism of action in targeting tumor cells. Moreover, some studies also analyzed the Theranostic potential of these treatments, via intra-tumoral accumulation which enhances current imaging modalities for diagnosis. Although, its relative novelty has limited the scope of this review, due to the small numbers of papers present implementing targeted therapy on thyroid carcinoma. Furthermore, only in vivo and in vitro studies were found testing different types of conjugated targeted therapies on thyroid cancer. Despite different targeting and therapeutic agents used for each study, all the studies reported positive selectivity on thyroid cancer cells, hence providing a number of different potential agents for further exploratory research.

Conclusion:

In conclusion, thyroid cancer has been an increasing problem worldwide with an incidence increase of about two times in the

past 5 years. Following those concerns, current treatments and medications are put to the test, with the constant dilemma of choosing between non-aggressive and aggressive approaches towards the current state of the carcinoma. Nonetheless, such treatment procedures were proven futile, with minimal results being shown as promising. However, with the recent breakthrough of personalized medicine, especially in targeted therapies, some studies have shown its potential alongside its theoretical approach in targeting specific tumor cells without diffusely damaging other cells. From this review, the included studies showed promising results with their high selectivity towards thyroid tumor cells. Furthermore, some studies also discovered and tested the conjugate's potential as a diagnostic tool, making this theranostic property superior to conventional therapies. However, due to the lack of recent clinical data on the efficacy of conjugated targeted therapies on human subjects, the authors recommend a full-fledge biosafety study to determine the conjugate's safety profile on human subjects. Afterwards, the author suggests the robust initiation of controlled clinical trials (in comparison to non-conjugated targeted therapies) to provide more baseline information

on the effectiveness of this treatment. Nevertheless, with the ongoing stalemate of thyroid cancer treatment (and other cancer in general), the authors feel that conjugated targeted therapies are truly the 'frontier' and 'future' of cancer treatment.

Declarations

Ethics approval and consent to participate

Not applicable.

Availability of data and material

Not applicable.

Conflict of interests

The authors declare no competing interest

Funding

Not applicable.

Authors' contributions

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References

1. Zhai M, Zhang D, Long J, Gong Y, Ye F, Liu S, et al. The global burden of thyroid cancer and its attributable risk factor in 195 countries and territories: A systematic analysis for the Global Burden of Disease Study. *Cancer Medicine*. 2021;10(13):4542–54.
2. Tsang VHM, Gild M, Glover A, Clifton-Bligh R, Robinson BG. Thyroid cancer in the age of COVID-19. *Endocrine-Related Cancer*. 2020 Nov;27(11):R407–16
3. Guan W, Liang W, Zhao Y, Liang H, Chen Z, Li Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J*. 2020 May;55(5):2000547.
4. Xu L, Bai Q, Zhang X, Yang H. Folate-mediated chemotherapy and diagnostics: An updated review and outlook. *J Control Release*. 2017 Apr 28;252:73–82.doi:10.1016/j.jconrel.2017.02.023.
5. Chen L, Zhao K, Li F, He X. Medullary Thyroid Carcinoma With Elevated Serum CEA and Normal Serum Calcitonin After Surgery: A Case Report and Literature Review. *FrontOncol*.2020Oct 27;10:526716.doi:10.3389/fonc.2020.526716.
6. Ham JC, van Meerten E, Fiets WE, Beerepoot LV, Jeurissen FJF, Slingerland M, et al. Methotrexate plus or minus cetuximab as first-line treatment in a recurrent or metastatic (R/M) squamous cell carcinoma population of the head and neck (SCCHN), unfit for cisplatin combination treatment, a phase Ib-randomized phase II study Commence. *Head Neck*. 2020 May;42(5):828–838. doi:10.1002/hed.26053.
7. Nguyen QT, Lee EJ, Huang MG, Park YI, Khullar A, Plodkowski RA. Diagnosis and treatment of patients with thyroid cancer. *Am Health Drug Benefits*. 2015 Feb;8(1):30–40. PMID:

- 25964831; PMCID:
PMC4415174.
8. Wilkes GM. Targeted Therapy: Attacking Cancer with Molecular and Immunological Targeted Agents. *Asia Pac J Oncol Nurs*. 2018 Apr-Jun;5(2):137-155.doi: 10.4103/apjon.apjon_79_17. PMID: 29607374; PMCID: PMC5863423.
 9. Nasiri H, Valedkarimi Z, Aghebati-Maleki L, Majidi J. Antibody-drug conjugates: Promising and efficient tools for targeted cancer therapy. *J Cell Physiol*. 2018 Sep;233(9):6441-6457. doi: 10.1002/jcp.26435. Epub 2018 Mar 25. PMID: 29319167.
 10. Crisci S, Amitrano F, Saggese M, Muto T, Sarno S, Mele S, Vitale P, Ronga G, Berretta M, Di Francia R. Overview of Current Targeted Anti-Cancer Drugs for Therapy in Onco-Hematology. *Medicina (Kaunas)*. 2019 Jul 28;55(8):414.doi:10.3390/medicina55080414. PMID: 31357735; PMCID: PMC6723645.
 11. Baudino TA. Targeted Cancer Therapy: The Next Generation of Cancer Treatment. *Curr Drug Discov Technol*. 2015;12(1):3-20. doi:10.2174/157016381266615060214 4310. PMID: 26033233.
 12. Nasiri H, Valedkarimi Z, Aghebati-Maleki L, Majidi J. Antibody-drug conjugates: Promising and efficient tools for targeted cancer therapy. *J Cell Physiol*. 2018 Sep;233(9):6441-6457. doi: 10.1002/jcp.26435. Epub 2018 Mar 25. PMID: 29319167.
 13. Lee YT, Tan YJ, Oon CE. Molecular targeted therapy: Treating cancer with specificity. *Eur J Pharmacol*. 2018 Sep 5;834:188-196. doi: 10.1016/j.ejphar.2018.07.034. Epub 2018 Jul 20. PMID: 30031797.
 14. Juweid ME, Hajjar G, Swayne LC, Sharkey RM, Suleiman S, Herskovic T, Pereira M, Rubin AD, Goldenberg DM. Phase I/II trial of (131)I-MN-14F(ab)2 anti-carcinoembryonic antigen monoclonal antibody in the treatment of patients

- with metastatic medullary thyroid carcinoma. *Cancer*. 1999 Apr 15;85(8):1828-42. doi: 10.1002/(sici)1097-0142(19990415)85:8<1828::aid-cnrcr25>3.0.co;2-h. PMID: 10223579.
15. Lin R, Ma B, Liu N, Zhang L, He T, Liu X, Chen T, Liu W, Liang Y, Wang T, Ni G, Liu X, Yang N, Zhang J, Yuan J. Targeted radioimmunotherapy with the iodine-131-labeled caerin 1.1 peptide for human anaplastic thyroid cancer in nude mice. *Ann Nucl Med*. 2021 Jul;35(7):811-822. doi: 10.1007/s12149-021-01618-3. Epub 2021 May 4. PMID: 33948902; PMCID: PMC8197720.
 16. Wang Q, Sui G, Wu X, Teng D, Zhu L, Guan S, Ran H, Wang Z, Wang H. A sequential targeting nanoplatfrom for anaplastic thyroid carcinoma theranostics. *Acta Biomater*. 2020 Jan 15; 102:367-383. doi: 10.1016/j.actbio.2019.11.043. Epub 2019 Nov 26. PMID: 31778831.
 17. Wang Y, Sui G, Teng D, Wang Q, Qu J, Zhu L, Ran H, et al. Low intensity focused ultrasound (LIFU) triggered drug release from cetuximab-conjugated phase-changeable nanoparticles for precision theranostics against anaplastic thyroid carcinoma. *Biomaterials Science*. 2019; 7: 196-210. Available from: DOI <https://doi.org/10.1039/C8BM00970>
 18. Jang S, Yu XM, Montemayor-Garcia C, Ahmed K, Weinlander E, Lloyd RV, Dammalapati A, Marshall D, Prudent JR, Chen H. Dysadherin specific drug conjugates for the treatment of thyroid cancers with aggressive phenotypes. *Oncotarget*. 2017 Apr 11;8(15):24457-24468. doi:10.18632/oncotarget.14904. PMID: 28160550; PMCID: PMC5421862.
 19. Niemelä E, Desai D, Niemi R, Doroszko M, Özliseli E, Kemppainen K, Rahman NA, Sahlgren C, Törnquist K, Eriksson JE, Rosenholm JM. Nanoparticles carrying fingolimod and methotrexate enables targeted induction of apoptosis and immobilization

of invasive thyroid cancer. Eur J Pharm Biopharm. 2020Mar;148:1-9.doi:10.1016/j.ejpb.2019.12.015. Epub 2020 Jan 7. PMID: 31917332.

20. Wang LY, Palmer FL, Nixon IJ, Thomas D, Patel SG, Shaha AR, Shah JP, Tuttle RM, Ganly I. Multi-organ distant metastases confer worse disease-specific survival in differentiated thyroid cancer. Thyroid. 2014 Nov;24(11):1594-9. doi: 10.1089/thy.2014.0173. Epub 2014 Sep 24. PMID: 25162180.
21. Harvey C. Ultrasound with microbubbles. Cancer Imaging. 2015 Oct 2;15(Suppl 1):O19. doi: 10.1186/1470-7330-15-S1-O19. PMCID: PMC4601836.

Appendix 1. Author Commentaries

N	o	Commentaries
1	Juw eid, 199 9	This study showcased the ability of targeted therapy as both a diagnostic and a therapeutic tool. It displayed the ability to detect unconfirmed positives metastatic thyroid cancer with relatively high sensitivity and specificity. Although due to its one-time dose, its efficacy could not be directly observed and only predicted by subject biomarkers, which displayed gradual betterment
2	Lin, 2021	Both caerin 1.1 and 131-I possess targeting and cytotoxic activity. Caerin 1.1 directly enters the cells and inhibit p-Akt activity, Targeting is apparently enhanced by 131-I which is naturally transported into thyroid cells using Sodium-Iodide symporter
3	Wa ng Qim eih ui, 201 9	Complete nanoparticles complex paired with irradiation yielded a complete cancer removal in Balb/c mice subjects. No pathological enzymes increase observed, proving biocompatibility. System also enabled diagnostic imaging enhancement by providing microbubbles created from perfluoropentane core (PFP)
4	Wa ng Yan	Complete complex was able to completely retard the tumor growth compared to incomplete complex and free drug (10-HCPT) of the same concentration. Moreover, local drug release could be

g, achieved by using LIFU, minimizing
 202 systemic effect. System also enabled
 0 diagnostic imaging enhancement by
 providing microbubbles created
 from perfluoropentane core (PFP)

5 Nie
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 a,
 2020 The study compared nanoparticles
 loaded with FTY720 with FTY720 &
 MTX cocktail. Although it showcased
 a similar cytotoxicity toward cancer
 cell, it significantly lowered the
 therapeutic agent cytotoxicity
 toward normal thyroid cell.

6 Jang,
 2017 Agent was highly efficient in inducing
 necrosis in all cancer groups, except the
 FTC133 and HTh7. This is due to the lack of
 dysadherin expression, suggesting high
 selectivity towards moderate-to-high
 dysadherin density malignancies.
 However, further study regarding
 biosafety is needed as CEN-106 is
 necrosis-inducing drugs and might
 triggers tumor lysis syndrome in human
 subject
