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Message from the ETA President

I am delighted to welcome you all to a new ETA initiative: *The Thyroidologist!*

I am sure that everyone is eagerly looking forward to our 44th Annual Meeting, which will be held "in person" on September 10th-13th in the wonderful cultural city of Brussels. It is the perfect opportunity to catch up and rekindle old friendships, develop our networks and embark on new collaborations. I know we will enjoy great science, wonderful food and the unique conviviality that we all enjoy as part of the ETA family. I, for one, cannot wait!

In this spirit of optimism and opportunity we launch *The Thyroidologist* under the leadership of Paula Soares from Porto. Together with an Editorial Board comprising Simone De Leo from Milan, Balazs Gereben from Budapest, Bijay Vaidya from Exeter, Lars Möller from Essen and Leonidas Duntas from Athens we have representation from across Europe covering the interests of pathology, thyroid cancer, basic laboratory science, clinical thyroidology and our trainees and fellows who embody the future of the ETA. On behalf of the ETA I would like to thank the outstanding Editorial Board team for their enthusiastic commitment and hard work in the beginning of what we hope will become a regular highlight for ETA members in the years to come.

The Thyroidologist aims to provide something for everyone that is different, informative, more informal and enjoyable for all thyroid obsessives! We wish to develop broad communication, expand collegiate friendship and embrace all ETA members by including diverse articles and content. Interviews with esteemed "big names" in thyroidology or with students and fellows embarking on their thyroid career can be included. We would like to give members the opportunity to showcase their institutions across Europe, providing brief articles and photographs. ETA announcements and recent thyroid-related news, highlights published in the *European Thyroid Journal*, or behind the scenes information relating to how the ETA is governed by Officers and the Executive Committee can be covered. There could be thyroid-related quizzes, crosswords, photographic competitions or even cartoons from talented ETA artists out there! Anything that highlights the passion for the thyroid that we all share and embrace across the ETA is possible.

This first issue is just a start – can I urge everyone to think what you would like to see included and make suggestions to the Editorial Board. I know there will be lots of ideas and plenty of talent among you all and we want everyone to have the opportunity to contribute. *The Thyroidologist* is for all of you to enjoy so please support the Editorial Board by sending in your ideas and content. We have a well-deserved reputation for superb clinical, translational and basic science and for a wonderful and culturally diverse ETA Annual Meeting that is built on co-operation and friendship. *The Thyroidologist* aims to expand our culture even more by bringing light reading, interesting content and amusement to coffee tables across Europe.



Graham Williams President of ETA



Message from the ETA Secretary

We are happy to proudly present the inaugural issue of The Thyroidologist, the new biannual electronic membership magazine of the European Thyroid Association. As you glance through you may at first wonder whether we actually need another periodical, what the idea is behind its release, and to whom specifically it is addressed. The Thyroidologist was in fact born with the inspiring and edifying goals of contributing to creating greater interconnectedness and more vigorous networking among ETA members, forming a link with our Newsletter issued annually in June, offering a forum for the exchange of ideas and information, providing listings of job opportunities/ offers, publishing interviews conducted by the Editorial Board with ETA members who stand out thanks to their contribution to the Association's work in thyroid research and development...and so much more!.... the whole bringing the members of the ETA much closer together and thereby expanding our horizons in knowledge, info, updates, and awareness.

The Thyroidologist is organised and coordinated by an outstanding and dedicated Editorial Board, whom I would like to warmly thank for their commitment to this project.

In this inaugural issue please note in particular the original and artistic cover created by Peter Crutchley, the provision of personal clinical experience and summaries of Guidelines through interviews with the authors, as well as excellent papers on recent clinical and basic research in thyroidology. This is an ETA magazine for the ETA members to be participated in, consulted, and embraced by us all.

Enjoy reading The Thyroidologist!



Leonidas Duntas Secretary of the ETA



Message from the Editorial Board

Dear colleagues,

It is with great pleasure that we welcome you to the first issue of *The Thyroidologist;* The Magazine of the European Thyroid Association!

We envisioned this space as a meeting place, strengthening the feeling of belonging to the European Thyroid Association, as well as to highlight all the areas, activities and achievements of those working in the field of thyroidology.

We search for the active participation of all the ETA members and many sections of the Magazine will be open to your suggestions, texts and opinions. *The Thyroidologist* will be published biannually and will have a set of rubrics that we hope will please our members.

In this issue, we have welcome messages from ETA president, Graham Williams and ETA Secretary, Leonidas Duntas.

We will have a main theme in each issue, and in the first issue, we celebrate the 25th anniversary of the discovery of the sodium/iodide symporter (NIS), for its importance for thyroid research and clinics. We are glad to present, in this issue, contributions from Nancy Carrasco, a pioneer in NIS discovery and Christine Spitzweg, who has a vast experience on clinical applications of NIS.

Peter Smith selects interesting facts recovered in ETA archives and shares with us the Historical Vignette. In the Literature Highlight section, we present a couple of papers from the European thyroid Journal – the official Journal of the ETA, selected by its editor-in-chief, Simon Pearce, and other pertinent papers recently published in other journals, selected by the editorial board.

ETA has an important societal role, and that was sadly reminded by the current stressful situation. Furio Pacini gives us his thoughts on radiation and thyroid cancer. We also include the recently launched ETA Statement with Information and recommendations for the general population and patients with thyroid disease in the event of nuclear emergency, prepared by the ETA Public Health Board and the statement concerning the war in Ukraine issued by the European Thyroid Association Executive Committee and the Public Health Board.

We would like to have a nice image relating to thyroid in each issue, so we invite all ETA members to contribute with an impressive image from your research or your clinics. In the present issue, we present a nice picture from Clara Alvarez's research laboratory.

It is very important to count with new ideas and projects from younger ETA members, so we will have a dedicated space to present their projects or mobility experiences, that we called the "Starters' Corner". In this issue, Gianni Gradii tells us about the Italian Thyroid Cancer Observatory (ITCO) network. We welcome ETA research grant recipients to tell us, in the "Winners' Corner", how their project idea arose, how they developed and if they encountered any e difficulties along the way. In this issue, we have a testimonial from Livia Lamartina, one of the winners of the ETA Research Grant in 2021.

Other rubrics will be revealed in the future issues of *The Thyroidologist*, but we urge you to take part in this project and share your ideas, opinions and views. We would be pleased to publish Letters to the Editor, as well as to receive your suggestions and comments at (THYROIDOLOGIST@endoscience.de).

A special thanks to all the colleagues who accepted our invitation to contribute to this first issue and made it possible to bring this inaugural issue in a short period.

We hope you enjoy reading the magazine!

The editorial board



Paula Soares



Balazs Gereben



Lars Moeller



Simone de Leo



Bijay Vaidya



Leonidas Duntas



Celebration of the 25th anniversary of the cloning the sodium iodide symporter (NIS)



Nancy Carrasco's biography

Nancy Carrasco is the Joe C. Davis Professor and Chair of the Department of Molecular Physiology and Biophysics at the Vanderbilt University School of Medicine. She obtained her M.D. and Master's in Biochemistry at the National Autonomous University of Mexico. Her cloning of the sodium/iodide symporter (NIS) has had numerous ramifications

for many fields, including structure/function of transport proteins, molecular endocrinology, gene transfer, cancer, and public health. She has received numerous awards, including the Pew Award; the Arnold and Mabel Beckman Foundation Award; the Maria Sibylla Merian Award (Germany); the European Thyroid Association's Merck Prize (Poland); the Rose Pitt-Rivers Lectureship at the British Endocrine Society Meeting (Scotland); and the Noun Shavit Award (Israel). She has served as president of the Society of Latin American Biophysicists. Dr. Carrasco was elected to the National Academy of Sciences in 2015 and to the National Academy of Medicine in 2020.

25 years later: cloning of the sodium iodide symporter

Nancy carrasco

Active I- transport into the thyroid gland is the first step in the biosynthesis of the thyroid hormones, the master regulators of intermediary metabolism. The I- transporter has been used in clinical medicine in the diagnosis and treatment of thyroid disease since 1946, but it had not been identified at the molecular level until 50 years later, when we isolated the cDNA encoding the transporter by functional expression in *Xenopus laevis* oocytes¹. The task was extremely challenging because there was no DNA sequence information for the molecule available at the time, and no antibodies against it. We dubbed the protein the Na⁺/I⁻ symporter (NIS), because it couples the inward transport of Na+ down its electrochemical gradient to the inward translocation of I- *against* its electrochemical gradient (with a 2 Na⁺: 1 I⁻ stoichiometry).

The impact of the cloning of NIS and the subsequent extensive research on it has been far-reaching. It has transformed NIS research into a field in its own right, generating dozens of publications a year. NIS is the key molecule at the centre of the single most effective internal radiation cancer treatment ever devised: radioiodide (¹³¹I⁻) treatment for thyroid cancer administered after thyroidectomy. The appeal of this therapy lies not only in its remarkable overall efficacy, but also in that it is specifically targeted to NIS-expressing cells, such as thyroid cancer cells, and so causes only relatively mild side effects. Since cloning NIS, we and others have made fundamental

discoveries about the role of NIS in physiology and pathophysiology and made key inroads into understanding its transport mechanism. The following is a partial list of our accomplishments. We have:

- proposed and experimentally validated a NIS secondary structure model with 13 transmembrane segments, an extracellularly facing N-terminus, and an intracellularly facing C-terminus.
- predicted, on the basis of our structure/function results, that NIS should have a fold similar to that of the prokaryotic leucine transporter LeuT, even though there is no sequence identity between them. This prediction was confirmed by the crystal structure of vSGLT, the bacterial homologue of the human Na+/ glucose cotransporter (SGLT1), which belongs to the same protein family (SLC5) as NIS.
- shown that NIS is located on the basolateral surface of thyroid cells, where it transports I⁻, and demonstrated that NIS transports I⁻ in tissues other than the thyroid (salivary glands, stomach, small intestine, and lactating breast), and also, significantly, in breast cancer, both in primary tumors and in metastases^{2,3}.
- investigated the regulation of NIS transcription and the protein's biogenesis and posttranslational modifications, and conducted a thorough electrophysiological analysis of NIS function.
- capitalized on the NIS mutations that have been identified in patients as causes of congenital I- transport defects (ITDs); uncovered the mechanisms by which many of these mutations affect NIS function; and determined the molecular requirements of NIS at specific positions.
- discovered that NIS activity is regulated by the KCNQ1-KCNE2 K⁺ channel.
- analyzed kinetic data using a new approach that has revealed the affinities of NIS for Na⁺ and I⁻, as well as the occupancies of *all* the species in the *outwardly* open conformation.
- developed a novel approach to analyzing binding data and applied it to Na⁺-driven transporters-providing biochemical information beyond the non-integer Hill coefficient.
- generated a NIS knockout mouse. Using these mice, we have shown that 1) an extremely high dietary supply of I⁻ forestalls severe hypothyroidism; 2) the pathogenesis of hypothyroidisminduced non-alcoholic fatty liver disease is driven by intra and extrahepatic mechanisms; and 3) the paradoxical lean phenotype of hypothyroid mice is marked by increased adaptive thermogenesis in the skeletal muscle.
- demonstrated that perchlorate (ClO_4^{-}) , a well-known NIS inhibitor found as a pollutant in numerous drinking water sources, is actually actively transported by NIS as an oxyanion substrate with an electroneutral 1 Na⁺ : 1 ClO₄⁻ stoichiometry, the first report of any transporter able to transport different substrates with different stoichiometries; and
- demonstrated that even at concentrations much lower (0.6 μM) than those that compete with I- for transport, ClO₄⁻ radically changes the mechanism of NIS-mediated I- transport by changing the driving force for transport from 2 Na⁺ to 1 Na⁺ and decreasing the apparent affinity of NIS for I⁻ at least 6-fold⁴. Less transport of I⁻ will result in decreased biosynthesis of thyroid hormones.



Celebration of the 25th anniversary of the cloning the sodium iodide symporter (NIS)

The availability of the NIS cDNA has made it possible for researchers to ectopically express NIS by gene transfer to be used as an imaging reporter in preclinical and translational gene therapy, and to render cancer cells susceptible to NIS-mediated radioiodide treatment.

The more we understand about the inner workings of NIS, the better equipped we will be to extend its clinical use beyond thyroid disease. To this end, its structure must be determined–another highly challenging task, given that NIS is an extremely hydrophobic protein. At the time of this writing, as we mark the 25 anniversary of the cloning of NIS, our group has succeeded in determining three structures of rat NIS (which shares 89% sequence identity with human NIS and has similar transport properties), by single-particle cryo-electron microscopy (cryo-EM): one with no substrates bound, one with 2 Na⁺ and 1 \vdash bound, and one with 1 Na⁺ and the oxyanion perrhenate bound⁵. These findings yield insights into how NIS selects, couples, and translocates anions and releases its substrates into the cytosol.



In summary, NIS has evolved from being an unidentified transport system, as it was 25 years ago, to being at the center of many fields, including structure/function of membrane transporters, molecular endocrinology, gene transfer, diagnostic imaging, public health, and cancer therapy, even beyond thyroid cancer. As we continue to push these various lines of inquiry forward, NIS research will, I predict, yield a great many more surprising and valuable findings, over the course of the next 25 years and beyond.

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Celebration of the 25th anniversary of the cloning the sodium iodide symporter (NIS)



Christine Spitzweg biography

Christine Spitzweg is professor of medicine and director of the Interdisciplinary Thyroid Center at the University Hospital of Ludwigs-Maximilians-University (LMU) in Munich, Germany. After completion of her training in Munich she spent three years at the Mayo Clinic in Rochester, MN, as a postdoctoral research fellow, and currently holds an academic joint appointment

with the Division of Endocrinology, Diabetes, Metabolism and Nutrition at the Mayo Clinic. She is a clinical scientist with a special focus on advanced thyroid cancer and endocrine oncology. Her basic research aims at investigation of the role of the sodium iodide symporter (NIS) as a novel theranostic gene as well as thyroid hormone regulation of mesenchymal stem cell biology. She has chaired the research committee and was a member of the Board of Directors of the American Thyroid Association. She is currently a member of the Board of Directors of the International Thyroid Oncology Group.

25 years after cloning sodium iodide symporter (NIS): the emerging role of NIS as a theranostic gene

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Based on its well characterized role in radioiodine imaging and therapy in differentiated thyroid cancer for the last 80 years, NIS represents one of the oldest examples of a theranostic gene allowing NIS-mediated molecular imaging using routine nuclear medicine imaging techniques such as radioiodine gamma camera, SPECT/CT or PET imaging followed by targeted radioiodide therapy. The cloning of rat NIS cDNA by N. Carrasco's team (1) followed by cloning of human NIS cDNA by S. Jhiang's team (2) in 1996, has not only been a milestone in thyroid physiology, but has also provided a powerful new reporter and therapy gene allowing the development of a promising antitumor gene therapy strategy based on image-guided selective NIS gene transfer into non-thyroidal tumors followed by therapeutic application of ¹³¹I or alternative radionuclides, such as ¹⁸⁸Re and ²¹¹At (Fig. 1) (3)



The concept of image-guided sodium iodide symporter (NIS) gene therapy

One of the pioneer studies, demonstrating the nuclear medicine and oncology communities the enormous potential of NIS as a new therapy gene, was performed in J.C. Morris' laboratory at the Mayo Clinc. The prostate specific antigen (PSA) promoter was used to selectively express NIS in prostate cancer cells resulting in tissue-specific androgen-dependent iodide uptake activity and selective killing by accumulated ¹³¹I in vitro and in vivo in stably NIStransfected prostate cancer cell xenografts as well as after viral in vivo NIS gene transfer using replication incompetent as well as replication competent oncolytic adenovirus vectors (3-6). The most widely studied oncolytic virus-based NIS gene therapy approach is taking advantage of the anticancer activity of measles virus using an attenuated MV vaccine strain derived from the Edmonston-B vaccine lineage (MV-Edm). MV-Edm-based oncolytic virus therapy approaches using NIS as reporter and/or therapy gene have been investigated in various cancers by the team of the Molecular Medicine Program at the Mayo Clinic, including multiple myeloma and ovarian cancer, and has entered clinical translation with several clinical trials ongoing (3, 7).

In addition to oncolytic viral approaches, C. Spitzweg's group in collaboration with P. Nelson and E. Wagner at the Ludwig-Maximilians-Universität in Munich has focused on the investigation of non-viral approaches with high promise for systemic NIS gene delivery. Several generations of polymer/NIS shuttle systems have demonstrated increasing efficiency and biocompatibility in various tumor models with excellent tumor specificity enhanced by coupling of tumor specific ligands (3, 8, 9). Based on their excellent tumor homing capacity, mesenchymal stem cells (MSC) genetically engineered to express NIS represent another highly promising tool for systemic delivery of the NIS gene deep into critical microenvironments of growing tumors (10). Tumor specificity was enhanced by the application of gene promotors activated by micromilieu-derived signals, such as hypoxia, TGFB/Smad, RANTES and angiogenesis-derived signals offering the possibility of tailoring the NIS gene therapy approach to the individual tumor milieu (9).



Celebration of the 25th anniversary of the cloning the sodium iodide symporter (NIS)

Also, combination of MSC-based NIS gene delivery with external beam radiation as well as hyperthermia was explored as powerful strategies to enhance the efficacy of MSC-based NIS gene therapy (9, 11, 12).

The question, that had been repeatedly asked from the very beginning of the NIS gene therapy era, is if lack of iodide organification in non-thyroid tumors is an obstacle to effective NIS gene therapy? The results outlined in the extensive preclinical studies in various non-organifying tumor entities, conclusively demonstrate that high tumoral levels of NIS expression when combined with the associated iodide recirculation effect can effectively compensate for a lack of organification (3). In addition, alternative radionuclides, such as the beta-emitter ¹⁸⁸Re or the alpha-emitter ²¹¹At, that are also transported by NIS offer the possibility of higher dose rates due to their higher energy and shorter half-life (188Re: physical half-life 16.7 h, average beta-energy = 0.764 MeV, mean path length 3.5 mm; ²¹¹At: physical half-life 7.2 h, average alpha energy 6.8 MeV, mean path length 65 nm) as compared to ¹³¹I (physical half-life 8 d, average beta-energy 0.192 MeV, mean path length 0.8 mm). The bystander effect resulting from the crossfire effect of the applied radionuclide (maximum path length of 2.4 mm for ¹³¹I and 32 mm for ¹⁸⁸Re) as well as a radiationinduced biologic bystander effect are major advantages of the NIS gene therapy approach providing a mechanism to compensate for the heterogenous transgene expression, that is associated with most viral and non-viral gene delivery techniques limiting therapeutic efficacy (3).

In addition to allowing the robust therapeutic application of radioiodine in non-thyroid cancer settings, these studies have also been able to take advantage of NIS as a sensitive reporter gene that allows temporal and spatial monitoring of vector biodistribution, replication, and elimination - critically important issues for preclinical development and clinical translation in gene therapy. NIS has many characteristics of an ideal reporter gene, it is highly homologous between human, rat and mouse, it reports only viable cells, it has not been found to inpart toxicity upon ectopic expression in nonthyroidal cells, and it represents a non-immunogenic protein with a well-defined body biodistribution and expression, that mediates the transport of readily available radionuclides, such as ¹³¹I, ¹²³I, ¹²⁵I, ¹²⁴I, 99mTc, ¹⁸⁸Re or ²¹¹At (3, 9, 13). With ¹⁸F-tetrafluoroborate (TFB), a new NIS PET tracer has entered the NIS arena that allows for significantly improved, high quality PET imaging as compared to standard ¹²⁴I, offering the potential for expanded development and application of NIS as reporter gene (13). NIS reporter imaging has been demonstrated to be a very useful tool to monitor the delivery and fate of adoptively transferred cells such as MSCs (as outlined above), dendritic cells and immune cells such as chimeric antigen receptor T cells and regulatory T cells. Within cell therapy trials, NIS reporter gene imaging provides an efficient means of non-invasive quantitative tracking of in vivo biodistribution and survival of cells at on-target tissues as well as off-target tissues as source of potential toxicity (3).

As one of the most exciting NIS chapters since its cloning 25 years ago, the application of NIS as a theranostic gene within a powerful gene therapy concept has made significant progress from local NIS gene delivery towards promising new applications in disseminated disease, in particular, through the use of oncolytic viruses, nonviral polyplexes, and genetically engineered MSCs as highly effective, highly selective and flexible gene delivery vehicles. The further development of these approaches will allow for expanded individualization of NIS gene therapy (Fig. 1). With the increasing importance of detailed analysis of cell fate and biodistribution within cell therapy trials such as the expanding CAR T cell therapy, NIS provides a reporter imaging platform that builds upon the 80 years of clinical experience in the application of NIS-based radioiodine imaging in thyroid cancer patients. The preclinical data provide a solid basis for clinical translation, as evidenced by the series of clinical trials currently underway.

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Image of the issue



Sodium/Iodide symporter (NIS) in a thyroid follicle. Enhanced NIS (red) expression after ten days of mild hypothyroidism. Nuclei are in blue. Expressed at the cytoplasm, NIS is concentrated at the plasma membrane of the basolateral pole of the follicular epithelium, in contact with the capillary.

(Credits Jesuina Graça-Fonseca, Alberto Pradilla-Dieste, Clara V Alvarez, CIMUS, Santiago de Compostela).



The year 2022 marks the 30th Anniversary of the Annual Meeting of the European Thyroid Association held in Dublin, Ireland from 20-25th of June, 1992. The Meeting under the joint patronage of Trinity College Dublin (TCD), University College Dublin (UCD), and the Irish Endocrine Society was held in TCD, which in 1992 was celebrating

Of course back in 1992 "Extra Thyroidal Activities" featured more prominently than they do in 2020's more restrictive atmosphere. The Dublin organisers were determined to live up to the reputation of traditional Irish hospitality. It is hoped that we went some way to discharging this responsibility and that delegates received a "Cead

the 400th Anniversary of its founding charter awarded by Queen Elizabeth 1 in 1592. Unfortunately the dates of the Dublin meeting clashed with the US Endocrine Society meeting in San Antonio, Texas but despite that, many US endocrinologists made heroic efforts to attend both meetings. As the Irish members of the ETA numbered two, myself and Michael Cullen, the Local Organising Committee (LOC) was four strong, the balance being made up of two highly efficient wives, Deirdre Smyth and Valerie Cullen who "volunteered" their services in the cause of Thyroidology. Although this small number made for a heavy work load, it had the advantage of limiting contrary opinions and facilitating instant decision making. The organisers had admirable support from the ETA President, the late Georg Hennemann and Secretary/ Treasurer Albert Burger. The meeting attracted 400 active participants together with 100 accompanying persons and



a feature was the presence of many Eastern European colleagues attending their first ETA meeting. Interestingly, the presentations reflected the scientific priorities of the day, autoimmunity, thyroid hormone action, thyroid cell biology with only minor focus on thyroid cancer which predominates in more recent times. Mile Failte" (one hundred thousand welcomes). I am encouraged to think we succeeded by the regular compliments I have received over the years commenting on the Irish evening (Ceili') held in UCD featuring Irish music, dancing and in particular the accompanying oysters and Guinness.



Peter Smyth, Dublin Chair ETA Archives Board



An interview: Furio Pacini



Biography of Dr. Furio Pacini

Dr. Furio Pacini is Professor of Endocrinology and Metabolism, Ex-Chairman of the Section of Endocrinology and Metabolism at the University of Siena, Italy. He was trained in medicine at the University of Pisa where he obtained the MD degree in 1973 and the postgraduate speciality in Endocrinology in 1977. As recipient of postdoctoral fellowship he pursued

thyroid research in the thyroid laboratory of Dr. Leslie J. De Groot at the University of Chicago (1980-1982). Back to Italy, he resumed his position in the Department of Endocrinology of the University of Pisa, where he directed a group of investigators principally devoted to research in the field of thyroid cancer and developed clinical and research activities which gained worldwide recognition. In 1996, he spent a sabbatical as Visiting Professor in the Department of Nuclear Medicine at the Institute Gustave Roussy, Villejuif (France). In the year 2002, he moved to the University of Siena as Professor of Endocrinology and Metabolism, Director of the Section of Endocrinology and Metabolism, where he created a new group of clinical and research fellows.

With his work spanning for more than 35 years, Dr. Pacini has contributed to the implementation of novel diagnostic and treatment protocols for the management of differentiated, anaplastic and medullary thyroid cancer. Of special interest are the research achievements on the relevance of serum thyroglobulin and calcitonin as tumor markers, the use of recombinant human TSH in the management of differentiated thyroid cancer, the assessment of clinical and molecular aspects of thyroid cancer, including post-Chernobyl radiation-induced thyroid cancer. The research activity of Dr. Pacini and his group is characterized by the use of hormonal, cellular and molecular approaches coupled with clinical observation, successfully bridging bench research and clinical practice. In recent years, he participated in task forces for the development of practice guidelines for the management of thyroid cancer, the one endorsed by the European Thyroid Association and those endorsed by the ATA.

For his contribution to thyroidology, Dr. Pacini has been in the Editorial Board of the Journal of Clinical Endocrinology & Metabolism and Senior Editor of Endocrine-Related Cancer, and Associate Editor of THYROID. Currently he is an associate Editor of European Thyroid Journal.

He has been awarded the "William Lees Lecture", Johns Hopkins University, Baltimore, in 2002; the "Martin Sonenberg Visiting Professor and Light of Life Foundation Award", Memorial Sloan-Kettering Cancer Center, New York in 2003; the 2008 ATA Paul Starr Award; the 2008 ETA Merck Prize. In September 2012, he was elected as "President Elect" of the European Thyroid Association. The scientific contribution of Dr. Pacini includes 238 scientific publications in peer-reviewed international journals. The average citation per paper is 44.6 and the average citation per year is 301. Dr. Pacini has an H index of 63 (by Web of Knowledge).

Interview

In recent days, the conflict in Ukraine has escalated. The fight close to the nuclear reactors in Ukraine and in particular at Zaporizhzhia, Europe's largest nuclear power plant, has triggered global fears of a major nuclear catastrophe. We had an opportunity to interview Prof. Furio Pacini, one of the leading experts on this topic.

Furio, can you explain what are the potential consequences of a nuclear accident?

As learned from the Chernobyl accident in Ukraine and the Fukushima disaster in Japan, major damage to nuclear reactors can release a huge amount of radioactive material into the atmosphere including radioiodine. The health consequences depend on the inhalation and the ingestion of contaminated food and water but the main determinant is the amount of radioactive contamination in a single individual.

The most at-risk organ, at least for a brief period, is the thyroid gland which is avidly incorporating iodine radionuclides once entered in the body through active mechanisms of uptake. As a consequence thyroid cancer can develop in the brief-medium-long term. The chance to develop thyroid cancer depends on the individual radiation dose to the thyroid. Children and adolescents carry a higher risk because their thyroid cells are rapidly dividing, the uptake of iodine is higher compared to adults and they drink much more contaminated milk than adults. After the Chernobyl accident, the number of children and adolescents developing thyroid cancer was very high and started to occur just 3-4 years after the accident because the release of radioactive iodine (short-lived isotopes and 131-iodine) was very, very high. However, it should be remembered that radioiodine has a short half-life and in about two months there is almost no radioactive iodine in the soil and the atmosphere provided that the reactor does not continue to release radioactive material after the first explosion. Of course, another type of solid cancer and hematological malignancies can occur but at a later stage and in less pronounced amounts

What precautions should be taken to reduce this risk of thyroid damage?

Immediately after a nuclear disaster, the local authorities should implement the distribution of stable iodine tablets (50 mg) to children and adolescents up to 18 years. In addition, the population (residing in a range of 30 Km from the epicenter) should be advised to stay inside and not to eat or drink stuff collected from the



An interview: Furio Pacini

contaminated areas. However, this indication depends also on the prevailing winds that can transport the radioactive cloud even farther than 30 Km. Monitoring of the radioactivity on the ground and air as well as measuring the radiation dose to the thyroid is of paramount importance to establish guidelines for intervention.

Do you believe we can do something from a logistic point of view to prevent these risks?

Prevention is based on the measures described above. In addition, the health authorities can decide whether or not to implement thyroid screening for the exposed population or for individuals at risk. This is not prevention, but early detection of thyroid nodules and cancer. Indiscriminate screening of the population means submitting to thyroid palpation and ultrasound the entire population in an affected area. Screening of individuals at risk means screening only individuals with a thyroid radiation dose above a certain threshold. The choice between these two methods of intervention is based on the thyroid radiation dose. The International Agency for Research on Cancer (IARC) in its Technical Publication no. 46 of 2018 (1), has set this threshold to 100-500 mGy or more. Below these levels, population screening will cause overdiagnosis with the risk overwhelming the benefits, as demonstrated after the Fukushima accident where the radiation dose was below such levels. On the contrary, population screening was effective in the case of the Chernobyl accident.

In case of a possible nuclear accident, how do you think it may impact cancer epidemiology and genetics?

Despite the above-mentioned guidelines intended to mitigate the possibility of risk exceeding the benefit, it is difficult to prevent the fear of the population that will press the authorities to have thyroid screening. However, we should understand that unjustified screening of a population will affect the epidemiology and the genetics of a disease (thyroid cancer) because of the well-demonstrated phenomenon of overdiagnosis. This has been very clearly shown in South Korea after the introduction of a program of generalized screening of the thyroid gland. The number of subclinical thyroid cancers detected in a few years was so disproportionate that the Government was forced to abandon the project (2).

Furio Pacini MD. University of Siena, Italy. pacini8@unisi.it

Reference

- 1. Thyroid Health Monitoring after nuclear Accidents. IARC Technical Publication no. 46, 2018. http://publications.iarc.fr.
- Worldwide Thyroid-Cancer Epidemic? The Increasing Impact of Overdiagnosis. Vaccarella S, Franceschi S, Bray F, Wild CP, Plummer M, Dal Maso L.N Engl J Med. 2016 Aug 18;375(7):614-7.



Recent highlights from European Thyroid Journal

Metabolic Changes after Radioiodine Correction of Grade 1 and Grade 2 Subclinical Hyperthyroidism

While subclinical hyperthyroidism is associated with several adverse health outcomes including atrial fibrillation, reduced bone mineral density and increased mortality, there is a lack of randomised trials that demonstrate a benefit from treatment. With this background, Dr Russo and colleagues from Brussels examined metabolic changes in 74 patients with endogenous subclinical hyperthyroidism. Following radioiodine treatment, they demonstrated increased BMI and serum cholesterol, particularly in patients with a fully suppressed TSH at baseline. Read the paper in full in our fully open access Journal

https://etj.bioscientifica.com/view/journals/etj/10/5/ETJ512734.xml

Prevalence and Treatment Outcomes of Marine-Lenhart Syndrome in Japan

Marine-Lenhart syndrome (MLS) is the unusual combination of one or more autonomously functioning nodule within the thyroid of a patient with Graves' disease. Dr Danno and coworkers from Kobe, have made a 14-year study of the condition across Japan. MLS was confirmed to be rare at just 0.25% of patients with Graves' disease. Treatment with radioiodine led to hypothyroidism in 43% of patients with MLS compared to just 9% with autonomously functioning thyroid nodules. Explore the full text of this paper:

https://etj.bioscientifica.com/view/journals/etj/10/6/ETJ510312.xml





Recent highlights from other journals

Long-term effects of T₃ Analogue Triac in MCT8 Deficiency

Monocarboxylate transporter 8 deficiency (also known as Allan-Herndon-Dudley Syndrome) is a rare condition caused by mutations in thyroid hormone transporter MCT8 and is characterised by severe neurodevelopmental delay and features of thyrotoxicosis in peripheral tissues. A previous open labelled 12-month clinical trial showed a beneficial effect of T3 analogue Triac in improving features of peripheral thyrotoxicosis in patients with MCT8 deficiency. Dr Geest and colleagues have now studied the long-term effects (up to 6 years treatment) of the drug in 67 patients from 33 centres in 18 countries. They found a persistent beneficial effect of Triac over the years in both adults and children with MCT8 deficiency. Read the full text of this paper:

J Clin Endocrinol Metab

https://academic.oup.com/jcem/article/107/3/e1136/6408637

Exposure to air pollution in late pregnancy and risk of congenital hypothyroidism

Recent studies have suggested that exposure to air pollutants during pregnancy could affect maternal and neonatal thyroid hormone levels. Now Dr Harari-Kremer and colleagues have analysed the data from the Israeli national screening programme for congenital hypothyroidism involving nearly 700,000 neonates and the data from the spatiotemporal modelling to show that exposure to traffic related pollution in the third trimester is associated with an increased risk of congenital hypothyroidism. Read the full paper:

Am J Epidemiol

https://academic.oup.com/aje/article/190/12/2630/6310595? login=true

No benefit of levothyroxine in euthyroid TPO-Ab positive women with recurrent pregnancy loss

Several previous observational studies have shown that thyroid peroxidase antibodies (TPO-Ab) positivity is associated with an increased risk of pregnancy loss. In this multi-centred, double-blind, placebo-controlled randomised controlled trial, Dr van Dijk and colleagues have examined whether levothyroxine increases the rate of live births in euthyroid pregnant women with TPO-Ab positivity and a history of recurrent pregnancy loss. They found similar rates of live births in the women treated with levothyroxine and placebo (50% vs. 48%, respectively), suggesting that there is no role for a routine use of levothyroxine in euthyroid women with TPO-Ab positivity and recurrent pregnancy loss. Read the full paper:

Lancet Diabetes Endocrinol

https://www.thelancet.com/journals/landia/article/PIIS2213-8587(22)00045-6/fulltext



ETA Public Health Board Statement

Nuclear emergency: Information and recommendations for the general population and patients with thyroid disease

Moreno-Reyes R, Feldt-Rasmussen U, Köhrle J, Gaspar da Rocha A, Bednarczuk T, Duntas LH.

Due to peoples', and particularly thyroid patients', increasing alarm as to the risk of a nuclear emergency, the European Thyroid Association Public Health Board, considers it necessary to issue a reminder concerning the guidelines on the use of potassium iodide (KI) tablets to protect the thyroid from radioactive iodine. Patients with treated thyroid disease should follow the same recommendations given to the general population. On the other hand, they should consult their physician so that their treatment may be adapted to the circumstances. Nuclear accidents release radioactive iodine into the atmosphere, which can be absorbed by the thyroid, increasing the risk of developing thyroid cancer. Babies and young children are at the highest risk, along with expectant mothers. Consequently, the target population for KI tablets is very young and pregnant women. The risk of thyroid cancer due to radiation exposure is much lower for persons over 40 years. KI administration protects the thyroid only from radioactive iodine and not from other radioactive substances or external radiation. This is why ingesting KI tablets should be accompanied by other protective measures, such as confinement (staying inside a building with doors and windows closed) and avoiding food and vegetables from contaminated regions. Even when a nuclear emergency occurs, KI administration is required ONLY when it is recommended by the local authorities. With regard to KI intake, timing is crucial since the tablets are effective for only 24 hours. Ideally and as is the case in many countries, a population living near a nuclear power plant at large should have KI tablets at home. There are, in addition, regulatory guidelines for authority storage in e.g., schools, fire departments, and other public places for distribution to the local population. Inadequate iodine intake from the daily diet is an issue in some population groups in many European countries, as pointed out by the Iodine Global Network and other organizations. In such conditions of low iodine intake, radioactive iodine uptake by the thyroid increases. Regarding children, the risk of thyroid cancer may be two to three times higher among those who are iodine-deficient as compared to children living in areas where iodine intake is adequate. Optimal iodine intake will not avert the need for KI administration, but may to some extent protect those who have not received KI. We also wish to warn against unauthorized intake of KI, particularly in areas with long-term low iodine intake and among patients with nodular goiters, who are liable to serious adverse effects through KI intake, such as thyrotoxicosis (e.g., as seen after iodine contrast investigations). The intake should therefore also, for this reason, be limited to absolutely necessary protective measures indicated by the authorities.

WHO SHOULD TAKE (EMERGENCY) KI TABLETS

- Once the competent authorities have confirmed the need for KI tablets, children and pregnant women should take the recommended KI dose. Adults under 40 years are at lower risk but still may benefit from KI intake.
- In addition to KI, other protective measures are usually necessary, such as confinement (staying inside a building with doors and windows closed) and avoiding the ingestion of contaminated food and drink (water, milk).
- In most cases, only one KI tablet will be sufficient.
- Patients with thyroid disease should follow the same recommendations given to the general population. They should seek medical advice when the emergency phase is over.

WHAT ARE THE RECOMMENDED KI DOSES

AGE	DOSE
0 – 1 months	6 mg
1 month – 3 years	
3 – 12 years	65 mg
>12 years	130 mg

KI 130 mg is equivalent to 100 mg iodine and the recommended dose is in agreement with the WHO recommendation.

HOW TO TAKE KI TABLETS?

- Dissolve the KI tablet in a small amount of water, then add this to a drink (juice, milk, water).
- For babies and children up to 2 years of age, the KI tablet needs to be crushed. The powder is dissolved in a small amount of lukewarm liquid, then additional liquid is added, for example, (breast) milk. The powder can alternatively be added to the child's meal.
- The resulting solution cannot be stored and must be taken immediately.

March 2022

https://www.eurothyroid.com/news/phb-statement-nuclearemergency.html



Statement concerning the war in Ukraine issued by the European Thyroid Association Executive Committee and the Public Health Board

One month has passed since Russian President Vladimir Putin shattered the peace in Europe by invading Ukraine. We are witnessing unending suffering in Ukraine along with the anguish of nearly four million refugees and an increasing number of crimes against humanity. The European Thyroid Association (ETA) strongly condemns the Russian invasion of Ukraine and expresses its full solidarity with the Ukraine population, demanding an immediate cessation of hostilities.

The ETA, as a medical and research Association, will undertake any effort, alone or in collaboration with affiliated societies, to send drugs and medical supplies to our colleagues in the war zones: we have specifically already discussed with our Corporate Members the delivery of endocrine drugs. We are also willing to donate funds to independent organisations committed to providing medical humanitarian assistance to people affected by the war.

March 2022

On behalf of the Executive Committee and the Public Health Board of the ETA

Leonidas Duntas Secretary of the ETA







Giorgio Grani

The Italian Thyroid Cancer Observatory (ITCO) network coordinates a multicenter, prospective, observational study on the clinical outcomes of thyroid cancer.

The web-based database was opened in 2013 at the Thyroid Cancer Center of the Sapienza University of Rome (the network's Coordinating Center). Since then, it has expanded to

include 50 other thyroid cancer centers in the country that joined the network. The database now includes prospectively collected data on more than 10 000 patients with histologically confirmed diagnoses of differentiated, medullary, poorly differentiated, and anaplastic thyroid cancer. Cases are eligible to be included in the database at the time of the initial treatment in the reporting ITCO center, or when the patient begins follow-up in a reporting center within 12 months after undergoing the initial treatment in a non-ITCO center. Each case record contains information on patient demographics and biometrics, circumstances of the diagnosis, tumor pathology, surgical and radioactive iodine treatments, as well as the results of periodic follow-up examinations. Sensitive data are encrypted, and the database is anonymously managed for statistical analysis.

The study protocol provides no guidance or restrictions in terms of patient management to the participating centers. So, the database is designed to provide a picture of real-world practices.

The primary outcome of the study is the rate of disease persistence or recurrence. This will be estimated at four main timepoints: 12, 36, and 120 months after the initial treatment. Potential predictors of persistence and recurrence will be also identified using different statistical approaches. Currently, the network collects data on about 1500 new patients every year.

The data collected from this database have already been used for scientific reports (Forleo R, et al. Thyroid. 2021; Grani G, et al. Thyroid. 2021; Lamartina L, et al. Endocr Relat Cancer. 2018; Lamartina L, et al. Thyroid. 2017.) and presented to multiple ETA Congresses (e.g., 40th Annual Meeting in Belgrade and 42nd Annual Meeting in Budapest).

Furthermore, the ITCO Network promotes educational activities and Continuing Medical Education events in Italy about thyroid nodules and cancer. These events are promoted through its website (http://www.itcofoundation.org) and social media (https://twitter. com/FoundationItco)





ETA Research Grant 2021



Livia Lamartina

Livia Lamartina is a Specialist Practitioner at Gustave Roussy Cancer Campus in Paris and she was one of the winners of the ETA Research Grant in 2021. Her project is entitled "Improving risk stratification in pediatric and adolescent differentiated thyroid Cancer".

What were the main difficulties that you faced in preparing your project? What would you advise to the new applicants?

My advice is to try to develop a project aimed at answering an unmet need and propose a methodologically rigorous project. Work with your team and ask the advice of your mentors and colleagues. Finding national or international partners are very good options too. The main difficulty is to propose an innovative translational project with a very limited budget but it is very important to have a starting budget to produce preliminary results in order to obtain larger grants.

Livia, can you tell us about your career so far?

I have performed my residency and the PhD in the University of Rome "Sapienza" under the mentorship of Sebastiano Filetti and Cosimo Durante. In this period, my research work was focused on thyroid cancer and thyroid nodules. I have also spent 18 months during my residency in the endocrine oncology and nuclear medicine unit of Gustave Roussy under the mentorship of Martin Schlumberger, Sophie Leboulleux and Eric Baudin and this gave me the opportunity to focus on refractory thyroid cancer and also to "discover" the other endocrine neoplasias such as pheo-paragangliomas, adrenal cancer and neuroendocrine tumors and cancers.

How did you develop the idea of your project?

I have always been interested in the issue of personalized medicine and several exciting data on re-differentiation strategies are emerging in recent years. Younger differentiated thyroid cancer patients are an interesting model of radioactive iodine sensitive disease and the optimal strategy for their treatment and follow up has not been established yet.

What do you think will be the impact of your study in the management of thyroid cancer in pediatric and adolescent patients?

We hope to contribute with some interesting information with a more thorough analysis of the large cohort of pediatric and adolescent differentiated thyroid cancer patients at Gustave Roussy. We would like to explore the predictive factors for response to radioactive iodine to identify those patients that could eventually be proposed a more "relaxed" treatment schedule, ideally to be proposed in the setting of a longitudinal clinical trial.

How do you think this prestigious achievement will affect your career?

Obtaining a research grant is an important achievement and I hope that it will help me to obtain other grants more easily in the future. I really thank the European Thyroid Association for recognizing the potential value of this project and my entire group for their work and support.



Upcoming Events

September 2022

European Thyroid Association

Thyroid Ultrasound Course – 2022 Basic course in diagnostic thyroid Ultrasound by the ETA-US Board 10 September 2022 in Brussels, Belgium Registration starts on 9 June 2022 and closes on 10 September 2022 https//www.eurothyroid.com

2022 World Endocrine & Obesity Conference (2022WEOC) with the collaboration of the TFI

September 09-10, 2022 https://endocrine.episirus.org/

44th Annual Meeting of the ETA

September 10-13, 2022 Brussels, Belgium Website: www.eta2022.com

ETA opportunities

Did you know that ETA has grant opportunities for clinical and basic projects, short-term stays and Travel Grants?

Check here those opportunities

ETA Project Research Grants – Two awards year (one basic and one clinical, 20.000 each)

Eligibility for Project Research Grant: ETA full members (i.e. not with provisional status) in good standing under the age of 40 (at the date of the close of submissions) and within 5 years of obtaining their research qualification (MD or PhD).

Submission at https://www.eurothyroid.com/about/research_grants.html

ETA Short-term clinical / Research Fellowship

Awards – Two awards year (10.000 each)

Eligibility for Short-Term Clinical/Research Fellowship Award: Applications should be from clinical thyroidologists or basic scientists who are ETA Junior Members in good-standing. Applicants should be no older than 35 years of age at the time of application and must hold a minimum of 12 months' ETA Junior Membership.

Submission at https://www.eurothyroid.com/about/research_grants.html

October 2022

Online Papillon Course on Thyroid Ultrasound

Online Course

- for beginners a 3-month course starting on September 15, 2022
- for experienced colleagues a 6-month course starting on December 1, 2022 September 15, 2022

The course has been endorsed by the ETA. A 50% discount is being offered to ETA members.

More information: http://thyrosite.com

91st Annual Meeting of the American Thyroid Association

October 19-23 Palais de Congres de Montreal Montreal, Quebec, Canada Website : www.thyroid.org

ETA Travel Grants – Up to 30 Grants (500€ each)

Travel Award grants are assigned to Junior ETA Members (<35 years of age) [not with provisional status], who are first authors of either oral or poster presentations at the Annual Meeting.

Application at http://www.eta2022.com/prizes.html



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