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Thyroid Cancer State of Science Conference

National Cancer Institute

Thyroid Cancer State of the Science Conference: Chernobyl and Beyond

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The statements, conclusions and recommendations contained in this document reflect both individual and collective opinions of the workshop participants and are not intended to represent the official position of the U.S. Department of Health and Human Services, the National Institutes of Health, or the National Cancer Institute.

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Acronym List

aCGH	array comparative genomic hybridization
ATC	anaplastic thyroid cancer
ATCC	American Type Culture Collection
BAC	bacterial artificial chromosome
CGH	comparative genomic hybridization
CTB	Chernobyl Tissue Bank
DCB	Division of Cancer Biology
DSV	diffuse sclerosing variant
DTC	differentiated thyroid carcinoma
EMT	epithelial-to-mesenchymal transition
ERK	extracellular signal-regulated kinase
FAK	focal adhesion kinase
FDG-PET	2-[18F] fluoro-2-deoxy-D-glucose and positron emission tomography
FFPE	formalin-fixed, paraffin-embedded
FNA	fine needle aspiration
FTC	follicular thyroid cancer
^{131}I	Iodine-131
MAP	mitogen-activated protein
MEK	MAP-ERK kinase
MEN	multiple endocrine neoplasia
MTC	medullary thyroid carcinoma
NCI	National Cancer Institute
NIH	National Institutes of Health
NIS	sodium-iodide symporter
OBBR	Office of Biorepositories and Biospecimen Research
PARP-1	poly (ADP-ribose) polymerase family, member 1
PDTC	poorly differentiated thyroid cancers
PI3K	phosphatidylinositol 3 kinase
PIK3CA	phosphoinositide-3-kinase, catalytic alpha polypeptide
PLGA	poly(lactic-co-glycolic acid)
PPARγ	peroxisome proliferator-activated receptor gamma
PTC	papillary thyroid cancer
RA	retinoic acid

RAI	radioactive iodine
RAR	retinoic acid receptors
RXR	retinoic x receptors
SEER	Surveillance, Epidemiology, and End Results
SNP	single nucleotide polymorphism
STR	short tandem repeat
T_3	triiodothyronine
T_4	thyroxine
TCGA	The Cancer Genome Atlas
Tg	thyroglobulin promoter
TKI	tyrosine kinase inhibitor
TPO	thyroperoxidase
TSH	thyroid-stimulating hormone
TZD	thiazolidinedione
Ukr-Am	Ukrainian-American Thyroid Study
V600E	valine-to-glutamic acid mutation at residue 600
VEGF	vascular endothelial growth factor

Thyroid Cancer State of the Science Conference: Chernobyl and Beyond

September 11–12, 2008

OPENING OF THE MEETING

This conference on the state of the science for thyroid cancer was chaired by Dr. James A. Fagin, Chief of the Endocrinology Service and member of the Human Oncology and Pathogenesis Program at Memorial Sloan-Kettering Cancer Center. Dr. Geraldine Thomas, Professor of Molecular Pathology at Imperial College London, served as the Chernobyl Chair, and Dr. Rihab R. Yassin, Program Director in the Division of Cancer Biology (DCB), National Cancer Institute (NCI), National Institutes of Health (NIH), who directs programs on the biology of thyroid cancer and the Chernobyl Tissue Bank (CTB), organized the conference and served as the NCI Chair.

The 2-day meeting was divided into four plenary sessions that featured perspectives on the state of the science for thyroid cancer from multiple stakeholders, the experience from research conducted on individuals exposed to the 1986 Chernobyl accident fallout, translational approaches in the treatment of thyroid cancer, and a panel discussion on the future of thyroid research. These sessions were interspersed with participant comments and questions and answers from the plenary session speakers.

Dr. Yassin welcomed participants to the conference and invited Dr. Daniel Gallahan, Deputy Director of the NCI DCB, to officially open the meeting. Dr. Gallahan reminded participants that the DCB funds research designed to understand the basic mechanisms of cancer and translate those findings into patient care. In alignment with the DCB's mission, he underscored the unique opportunity that exists today in thyroid cancer research given the resources developed as a result of the Chernobyl accident and the molecular skills available to interrogate this disease.
Dr. Gallahan also thanked participants for their attendance and organizers for their efforts in planning this landmark conference. Dr. Yassin further explained the purpose of this conference: To serve as the scientific platform for the review, dissemination, and exchange of research information concerning thyroid cancer with the objective of advancing the understanding of the molecular mechanisms underlying thyroid cancer formation, providing new avenues for future treatments, and furthering collaboration between thyroid cancer scientists. She added that an important conference objective is to identify unexplored or underdeveloped areas and directions in thyroid cancer research to guide the DCB research priorities in coming years. Dr. Yassin then invited Dr. Fagin to initiate the first session of the conference.

PLENARY SESSION I: THYROID CANCER STATE OF THE SCIENCE

MODERATOR: James A. Fagin, M.D., Memorial Sloan-Kettering Cancer Center

Chair's Perspective: Thyroid Cancer Science—Where Does the Field Stand?

James A. Fagin, M.D., Memorial Sloan-Kettering Cancer Center

Dr. James Fagin thanked Dr. Yassin for organizing the conference and briefly reviewed the agenda. He then provided an overview on the state of thyroid cancer research.

Epidemiology of thyroid cancer. There is a sharp increase in the incidence of papillary thyroid cancer (PTC) in the past 30 years, and many of these cases represent early stage disease. Radioactive iodine (RAI) is traditionally used post-operatively as adjuvant therapy for PTC; however, clinicians differ markedly in their approach to treat patients with low-grade disease. Many patients continue to receive RAI despite the fact that multiple national professional society guidelines severely caution against its indiscriminate use, in part because of questionable effectiveness, as well as growing concerns about the risk of development of secondary cancers.

A recent meta-analysis attempted to address whether adjuvant treatment with iodine-131 (^{131}I) is beneficial in preventing recurrences of low grade differentiated thyroid cancer.[1] The efficacy of RAI in diminishing locoregional recurrences of differentiated thyroid cancer is at best modest, and not found in all groups, and treatment with RAI does not prevent development of distant metastases. Furthermore, a 2008 publication by Brown and colleagues showed a minor but significant excess risk of development of secondary primary nonthyroidal cancers in patients treated with adjuvant ^{131}I.[2] In the past, the NCI has chosen not to sponsor prospective clinical trials for early-stage thyroid cancer largely due to the low mortality rate of the disease. However, the potential impact of RAI therapy on the generation of secondary primary cancers merits reconsideration of this decision.

Therapeutic targets in thyroid cancer. Potential therapeutic targets in thyroid cancer include those that are intrinsic to tumor cells; i.e., oncoproteins activated by germline or somatic mutations, and those that pertain to the tumor microenvironment. As oncoprotein activity is thought to be required for cancer cell viability, pharmacological or genetic abrogation of the activity of the oncoprotein results in cancer cell death. The critical role in tumor sustenance provided by the tumor microenvironment also opens therapeutic opportunities, such as those directed against tumor angiogenesis. In the future, strategies designed to interfere with lymphangiogenesis, tumor-associated macrophages, and mesenchymal stem cells may also offer promise. The microenvironmental targets are of particular interest to the thyroid cancer research community because many of the compounds that are active in clinical trials share the property of inhibiting kinase insert domain receptor (KDR), a vascular endothelial growth factor (VEGF) receptor.

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[1] Sawka AM, Brierley JD, Tsang RW. An updated systematic review and commentary examining the effectiveness of radioactive iodine remnant ablation in well-differentiated thyroid cancer. *Endocrinol Metab Clin N Am.* 2008;37(2):457-480.

[2] Brown AP, Chen J, Hitchcock YJ, et al. The risk of second primary malignancies up to three decades after the treatment of differentiated thyroid cancer. *J Clin Endocrinol Metab.* 2008;93(2):504-515.

Well-differentiated thyroid cancer (i.e., papillary [PTC] and follicular thyroid cancer [FTC]) represent more than 80 percent of all thyroid cancer cases. Mutations of effectors that signal along the mitogen-activated protein (MAP) kinase pathway are critical for PTC initiation, and among these, BRAF mutations are the most common. In contrast, RAS gene mutations predominate in FTCs. Survival of patients with well differentiated PTC or FTC is close to normal. Poorly differentiated thyroid cancer (PDTC) and anaplastic thyroid cancer (ATC), however, are more serious with a median survival of 3.5 years and 6 months, respectively. Based on these facts, Dr. Fagin's laboratory has recently concentrated on defining the genetic abnormalities in the most severe forms of thyroid cancer.

To identify the predominant oncogenic mutations in PDTC, Dr. Fagin and collaborators interrogated 111 different mutations that affect relevant oncogenes via mass spectrometry genotyping of human tumors. PDTC was found to be associated with mutations in all three RAS genes but less commonly with BRAF mutations. However, patients with BRAF mutations had higher cause-specific mortality. BRAF mutations were also predominant in ATC.

In another study performed in the Fagin lab in collaboration with Drs. Tuttle and Ghossein (unpublished), a comparison was conducted of the genetic profiles of encapsulated PDTC (thought to carry a good prognosis) and radioiodine refractory, 2-[18F] fluoro-2-deoxy-D-glucose (FDG)- positron emission tomography (PET) scan positive, thyroid carcinoma lesions. In the encapsulated PDTC tumors, BRAF mutations were rare while RAS mutations were predominant. In FDG-PET scan positive thyroid carcinoma lesions, BRAF mutations prevailed both in metastatic and primary lesions. Finally, activating mutations of the genes encoding the alpha catalytic subunit of phosphoinositide-3- *kinase* (PIK3CA*)* and AKT1, a pleckstrin homology domain mutation not previously reported in thyroid cancer, were found to coexist with BRAF mutations in patients with advanced thyroid cancer. The role of PIK3CA amplification remains to be elucidated, however.

In concluding this portion of his presentation, Dr. Fagin commented that tumor angiogenesis is relatively understudied in thyroid cancer and deserves more attention.

Oncogene studies in animal models of thyroid cancer. A relatively simple manner of interrogating oncogene function in thyroid cancer is through transgenic approaches, in which the oncogene expression is induced using the thyroglobulin promoter (Tg). This approach, however, results in overexpression of the oncoprotein. To achieve endogenous expression of oncogenes in mice, the Fagin lab used mice with a latent allele of the most common BRAF mutation, a valine-to-glutamic acid mutation at residue 600 (V600E), which were generated by Marais and Pritchard (LSL-Braf).[3] The latent BRAF allele was activated in thyroid cells by crossing the mice with thyroperoxidase (TPO)-Cre mice, provided by Dr. Shioko Kimura at NCI. Expression of BRAF activates phosphorylated extracellular signal-regulated kinase (pERK), and by 5 weeks of age, there was 100% penetrance of PTC with ~70% of *TPO-Cre/LSL-Braf*^{V600E} mice having invasive cancers. It may be that cancer penetrance is robust in this model because endogenous expression of BRAF^{V600E} causes hypothyroidism. Expression of genes encoding key molecules

[3] Mercer K, Giblett S, Green S, et al. Expression of endogenous oncogenic V600EB-raf induces proliferation and developmental defects in mice and transformation of primary fibroblasts. *Cancer Res.* 2005;65:11493-11500.

required for thyroid hormone biosynthesis—which in turn are controlled by a family of transcription factors expressed in thyroid cells, including Pax8—is knocked down in these animals. This is not due to impairment of thyroid gland development, as acute activation of oncogenic BRAF *in vivo* beginning at 5 weeks of age recapitulates all aspects of the phenotype. The mechanism of the effects of BRAF on thyroid gene expression is unknown. This is not a mouse-specific phenomenon; human thyroid cancers with BRAF mutations have decreased sodium-iodide symporter (NIS), Tg, and TPO compared to cancers with wild-type BRAF, and are more commonly refractory to RAI.[4,5]

Dr. Fagin then presented current work that focused on determining how thyroid-stimulating hormone (TSH) cooperates with BRAF in tumorigenesis. Supporting evidence for this investigative effort came from recent epidemiological studies on biopsies from patients with thyroid nodules.[6,7] Patients with malignant tumors had higher TSH levels at the time of diagnosis, suggesting that even modestly elevated TSH levels may promote transformation. In the mouse model, oncogenic BRAF was expressed at endogenous levels. When TSH was suppressed at 4 weeks of age via treatment with levothyroxine, PTC histology remained unaffected. When animals were treated at an earlier age and TSH production was suppressed, the growth of the thyroid cancers was markedly diminished. Dr. Fagin also demonstrated that the thyroid cancer phenotype is much more severe when both oncogenic BRAF and homozygous *Pten* (phosphatase and tensin homolog) deletion are targeted to the thyroid. None of these animals survived beyond 12 days of age, and all had anaplastic or poorly differentiated thyroid cancers.

Dr. Fagin then added that there is a significant interest in the research community to develop compounds that disrupt the MAP kinase pathway. Sorafinib, which is probably a weak inhibitor of RAF, may also target other kinases and demonstrate activity against the disease. Data from work conducted in thyroid cancer cell lines by Rebecca Leboeuf and Roberta Malaguarnera (please reference 55) confirms that cell lines with BRAF mutations are exquisitely sensitive to MEK inhibitors, whereas those with RAS mutations exhibit variable responsiveness. AZD6244, a MEK inhibitor, is also in trials for thyroid cancer.

In closing, Dr. Fagin presented exciting data on mammalian target of rapamycin (mTOR)—a serine/threonine protein kinase that regulates cell growth, proliferation, motility, survival, protein synthesis, and transcription. mTOR is activated by TSH signaling through cyclic adenosine monophosphate (cAMP), but when mTOR activity is blocked with rapamycin, the effects of TSH on cell growth are inhibited. In thyroid cancers, control of mTOR activity remains critical, yet is no longer dependent on cAMP but rather on signals from the MAPK and phosphatidylinositol-3-kinase (PI3K) pathways.

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[4] Durante C, Puxeddu E, Ferreti E, et al. BRAF mutations in papillary thyroid carcinomas inhibit genes involved in iodine metabolism. *J Clin Endocrinol Metab*. 2007;92(7):2840-2843.

[5] Xing M. BRAF mutation in papillary thyroid cancer: pathogenic role, molecular bases, and clinical implications. *Endocrn Review.* 2007;28(7):742-762.

[6] Boelaert K, Horacek J, Holder RL, et al. Serum thyrotropin concentration as a novel predictor of malignancy in thyroid nodules investigated by fine-needle aspiration. *J Clin Endocrinol Metab.* 2006;91(11):4295-4301.

[7] Haymart MR, Repplinger DJ, Leverson GE, et al. Higher serum thyroid stimulating hormone level in thyroid nodule patients is associated with greater risks of differentiated thyroid cancer and advanced tumor stage. *J Clin Endocrinol Metab.* 2008;93(3):809-814.

Dr. Fagin concluded his presentation by stating that a better understanding of other signals is needed to design inhibitors more effectively. This can be achieved by combining human and mouse genetics with functional studies in cell lines, and then entering the clinical trials realm.

Understanding the Rise in Thyroid Cancer Cases: Not as Simple as It Looks

Louise Davies, M.D., Dartmouth School of Medicine

Dr. Louise Davies began by informing participants that thyroid cancer is currently the fastest growing cancer diagnosed in the United States.[8] While medullary thyroid carcinoma (MTC) and ATC incidence rates remain low, and slight fluctuations are observed in FTC incidence (as a result of changes in diagnostic criteria), a marked increase in PTC incidence is responsible for the rise in thyroid cancer cases. Nevertheless, the overall thyroid cancer mortality rate, 0.5 deaths per 100,000 people per year, has remained unchanged since 1975.

Dr. Davies proposed that the rising PTC incidence is likely due to greater detection of subclinical disease. A key piece of evidence supporting this assertion comes from autopsy studies indicating that subclinical PTC is common. For example, a study conducted by Harach and colleagues in 1985 showed that a third of the thyroid glands examined had PTC, with tumors ranging up to 1.5 cm in size, and twenty-eight percent of glands had multiple cancer types.[9] Additional evidence supporting this subclinical reservoir theory comes from a comparison of PTC incidence in 1988 versus 2003 by tumor size in patients and deceased individuals. Based on data obtained from pathology reports, a 2 percent rise in PTC incidence is due to tumors 5 cm or larger, 12 percent from tumors 2–5 cm, and 86 percent from tumors measuring 2 cm or less (with more than half of the increase due to tumors measuring less than 1 cm in diameter).

Several events may have contributed to the increase in PTC incidence. A report released by the NCI in 1976 addressed the effects of radiation used as medical treatment for a variety of conditions between 1920 and 1960. In addition, ultrasound gained importance in the 1990s, as a result of the recognition that it was useful in obtaining better fine needle aspirates. Thus, the incidence of thyroid cancer is increasing due to a rise in PTC and greater detection of small (less than 2 cm) tumors.

Thyroid cancer overdiagnosis, the detection of cases that would not be clinically evident in a patient's life, is the end result of a substantial reservoir of subclinical PTCs and stable mortality rate. This phenomenon, also observed in other cancers such as prostate cancer, is an important concept because masses of the thyroid gland are found in more than 65 percent of asymptomatic individuals, and small PTCs are often treated with a total thyroidectomy, which may not be the best option for small tumors given the need for a lifetime of thyroid hormone replacement. A question to be considered is whether every PTC detected should be treated and the impact of such action. Based on Surveillance, Epidemiology, and End Results (SEER) data, more than 31,000 thyroid cancer cases were treated between 1973 and 2004 (i.e., partial or total thyroidectomy with or without radiation), while 467 patients received no treatment. Localized

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[8] Davies L, Welch HG. The increasing incidence of thyroid cancer in the U.S.: 1973-2002. *JAMA*. 2006;295(18):2164-2167.

[9] Harach HR, Franssila KO, Wasenius VM. Occult papillary carcinoma of the thyroid. A "normal" finding in Finland. A systematic autopsy study. *Cancer*. 1985;56(3):531-538.

PTC-specific survival (i.e., the probability over time of surviving the cancer) for both groups was high (96 and 98 percent survival at 20 years for the untreated and treated groups, respectively). Ten-year cancer-specific survival data showed that survival was the same for patients who were treated and those who declined treatment. However, in comparing overall survival curves for the treated and untreated groups, a significant number of deaths in the untreated group occurred in the first year due to the high competing risk by other causes. Individuals who survived had the same relative health status as those in the treatment group. Although a shortcoming of the SEER dataset is that only data on initial treatment is collected (i.e., if treatment is not completed within a 4-month window, the person is classified as having no treatment), the data support the recommendation that patients should be monitored before performing surgery.

In conclusion, a significant subclinical reservoir of PTCs is being detected, and many of these cases may not become symptomatic during the patients' lifetimes. Whether treatment is immediate or delayed, undertaken or declined, thyroid cancer survival is excellent; only a 2-percent mortality difference exists between treated and untreated groups. In contrast, surgery has inherent risks. Complications of thyroidectomy include permanent vocal cord paralysis in 1.7 percent of patients and permanent hypoparathyroidism in 5 percent of patients. In the future, more small cancers will continue to be detected, and more people will undergo surgery, which may not be in their best interest. Next steps include determining which PTC requires surgery, particularly when considering small, asymptomatic thyroid lesions.

Mechanisms of Papillary Thyroid Cancer Invasion

Matthew D. Ringel, M.D., The Ohio State University

Dr. Matthew Ringel's presentation focused on mechanisms of PTC progression, specifically on signaling pathways involved in disease progression, global analysis of PTC invasion, and the role of P21-activated kinase. Generally, well-differentiated thyroid cancers are treated surgically and via targeted therapy to the TSH receptor and NIS uptake. As the disease progresses, patients are treated with more TSH receptor suppression and RAI. However, data show that the treatment paradigm should be targeted to both the oncogene and secondary pathways of activation; i.e., progression targets. Several signaling pathways are activated *locally* in thyroid tumorigenesis and progression; thus, potential oncogenic targets for aggressive disease therapy include RET/PTC, BRAF, and Ras signaling pathways, as well as the PI3K/Akt pathway.

To determine which pathways are relevant in aggressive thyroid cancers, Dr. Ringel's group conducted an immunohistochemical analysis of follicular adenomas, follicular carcinomas, papillary carcinomas, and adjacent normal tissues from 75 of 78 tumors.[10] Results showed that thyroid cancer invasion is a complex process that involves a number of signaling pathways, including AKT and ERK and depends on both the initiating oncogene and secondary changes (e.g., mutations) that remain to be defined. Akt and p27 are overexpressed in FTCs and invasive regions of PTCs (with the notable exception of cancers with $BRAF^{V600E}$), and interplay of Akt and p27 is functionally important in mesenchymal cancer cell migration.

[10] Vasko V, Saji M, Hardy E, et al. Akt activation and localisation correlate with tumour invasion and oncogene expression in thyroid cancer. *J Med Genet*. 2004;41:161-170.

To verify the above findings, the investigators undertook a global assessment of invasion in thyroid cancer via microarray studies.[11] RNA was isolated from central and invasive tumor regions of seven widely invasive PTCs as well as normal tissue. Ingenuity™ Pathway Analysis showed that, in comparison to central regions of the tumor, integrin and PI3K/Akt signaling pathways were overrepresented in the invasive front. This finding pointed to a process known as epithelial-to-mesenchymal transition (EMT), which occurs when epithelial cells morphologically and behaviorally change and develop mesenchymal cell characteristics; e.g., increased motility and reduced contact inhibition. EMT has been implicated as functionally important in the process of cancer invasion and metastasis. A quantitative real-time polymerase chain reaction (RT-PCR) study using sequence-specific probes confirmed these data and that array underplayed the observed gene expression profile differences. A larger, second confirmatory study involving patients with PTC, 20 with local invasion, and 24 with lymph node metastasis also was conducted. Data from this study suggested that EMT is a common event in PTC invasion regardless of the initiating oncogene and may represent a target for progressive thyroid cancer. Vimentin, a polypeptide that copolymerizes with other subunits to form intermediate filaments in mesenchymal cells, also appears to play an important functional role in initiating and maintaining mesenchymal features in thyroid cancer cell lines *in vitro*. Finally, vimentin and osteopontin, an extracellular structural protein overexpressed in a variety of cancers, are regulated by similar pathways in cancer cells (p21-activated kinases and small G-proteins). Currently, novel agents targeting these pathways are being tested.

Molecular-Based Therapeutics of Advanced Thyroid Cancer: Nuclear Hormone Receptors, Kinase Signaling, and Cell Line Integrity

Bryan R. Haugen, M.D., University of Colorado

Dr. Bryan Haugen began his presentation by describing responses to retinoids in several clinical studies. Cumulatively, only 20 to 30 percent of ATC, PTC, and FTC patients treated for 6 weeks with 13-*cis* retinoid acid (RA), a preligand for nuclear hormone receptors, demonstrated an increase in RAI uptake; i.e., decreased growth and proliferation.[12,13,14,15,16,17,18,19] To predict response or resistance to treatment, nuclear hormone receptor expression was studied in a panel

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[11] Vasko V, Espinosa AV, Scouten W, et al. Gene expression and functional evidence of epithelial-to-mesenchymal transition in papillary thyroid carcinoma invasion. *Proc Natl Acad Sci U S A*. 2007;104:2803-2808.

[12] Börner AR, Simon D, Müller-Gärtner HW. Isotretinoin in metastatic thyroid cancer. *Ann Intern Med*. 1997;127(3):246.

[13] Simon D, Koehrle J, Reiners C, et al. Redifferentiation Therapy with Retinoids: Therapeutic Option for Advanced Follicular and Papillary Thyroid Carcinoma. *World J Surgery*. 1998;22:569-574.

[14] Grünwald F, Pakos E, Bender H, et al. Redifferentiation Therapy with Retinoic Acid in Follicular Thyroid Cancer. *J Nucl Med*. 1998;39:1555-1558.

[15] Grünwald F, Menzel C, Bender H, et al. Redifferentiation Therapy-Induced Radioiodine Uptake in Thyroid Cancer. *J Nucl Med*. 1998;39:1903-1906.

[16] Koerber C, Schmutzler C, Rendl J, et al. Increased I-131 uptake in local recurrence and distant metastases after second treatment with retinoic acid. *Clin Nucl Med*. 1999;24(11):849-851.

[17] Simon D, Körber C, Krausch M, et al. Clinical impact of retinoids in redifferentiation therapy of advanced thyroid cancer: final results of a pilot study. *Eur J Nucl Med Mol Imaging*. 2002;29(6):775-782.

[18] Grüning T, Tiepolt C, Zöphel K, et al. Retinoic acid for redifferentiation of thyroid cancer--does it hold its promise? *Eur J Endocrinol*. 2003;148(4):395-402.

[19] Short SC, Suovuori A, Cook G, et al. A phase II study using retinoids as redifferentiation agents to increase iodine uptake in metastatic thyroid cancer. *Clin Oncol*. 2004;16:569-574.

of thyroid cancer cell lines. Of the multiple isoforms of retinoic acid receptors (RARs) and retinoic x receptors (RXRs), RARβ and RXRγ were found to be differentially expressed.[20] Proliferation assays conducted with TTNPB (RAR synthetic ligand) and LG346 (RXR synthetic ligand) showed that proliferation responses to these agents were directly related to receptor expression levels. RARβ and RXRγ expression also was variable in human thyroid cancer tissues representing PTC, FTC, ATC, and follicular thyroid adenoma. These findings support the hypothesis that patients with higher expression of these receptors respond to therapy, while those who only express one receptor or a low level of both receptors do not. A clinical trial is underway with RXR-specific retinoid for growth inhibition of progressive tumors in patients with advanced thyroid cancer.

Dr. Haugen's group also studied the DRO cell line, which is unresponsive to RAR but highly expresses peroxisome proliferator-activated receptor gamma (PPARγ), a nuclear hormone receptor known to slow tumor growth in many cancers upon stimulation. Treating the cell line with retinoid agonist LG1069 alone or with thiazolidinediones (TZDs), which induce PPARγ, slowed tumor growth. Together, LG1069 and TZD had a synergistic effect, halting tumor cell growth. The same results also were observed in a mouse xenograft model. To discern the mechanism of resistance, cell lines were made resistant to these ligands or their combination. Cell lines desensitized to both ligands were resistant to all therapies, as expected, but cell lines desensitized to one of the ligands were resistant to the other ligand and the combination therapy. Further studies showed that PPARγ expression progressively decreased as resistance to treatment increased and was responsible for this effect. Results were confirmed via a xenograft model[21] and together have led to a clinical trial with a new compound, CS7107, plus paclitaxel for advanced thyroid cancer therapy.

Dr. Haugen then briefly addressed the issue of cell line integrity. He reported that as many as 36 percent of cell lines had been mischaracterized. Consequently, the NIH issued a notice that cell line authentication must be accompanied with grant applications. Three groups, including Dr. Haugen's, conducted a comprehensive analysis of 40 thyroid cancer cell lines.[22] Using short tandem repeat (STR) profiling (and Affymetrix 250K single nucleotide polymorphism [SNP] array to confirm results), it was shown that although some cell lines were in fact derivatives of the TPC-1 (thyroid cancer) cell line, others were derivatives of colon cancer or melanoma cell lines. Based on these findings, a review of the results of the above-described studies was conducted. Dr. Haugen and his collaborators concluded that their findings were still relevant at the molecular level and, therefore, it was valid to move forward with clinical trials.

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[20] Haugen BR, Larson LL, Pugazhenthi U, et al. Retinoic Acid and Retinoid X Receptors Are Differentially Expressed in Thyroid Cancer and Thyroid Carcinoma Cell Lines and Predict Response to Treatment with Retinoids. *J Clin Endocrinol Metab*. 2004;89:272-280.

[21] Copland JA, Marlow LA, Kurakata S, et al. Novel high-affinity PPARgamma agonist alone and in combination with paclitaxel inhibits human anaplastic thyroid carcinoma tumor growth via p21WAF1/CIP1. *Oncogene*. 2006;25:2304-2317.

[22] Schweppe RE, Klopper JP, Korch C, et al. DNA Profiling Analysis of 40 Human Thyroid Cancer Cell Lines Reveals Cross-Contamination Resulting in Cell Line Redundancy and Misidentification. *J Clin Endo Metab*. 2008;93(11):4331-4341.

In closing, Dr. Haugen described potential new therapeutic targets for thyroid cancer involving MEK-ERK and Src/focal adhesion kinase (FAK) signaling pathways, both of which play a central role in cell survival, proliferation, and adhesion/migration. Through a series of cell line experiments, it was shown that although MEK inhibits thyroid cancer cell growth, it does not affect phosphorylated FAK levels. In turn, the Src/FAK complex does not signal through the MAP kinase pathway, of which MEK is part. The identification of a novel signaling pathway in FAK expression and activation continues to be explored for targeted therapeutics in thyroid cancer. Already, a Src inhibitor that may be useful in treating advanced thyroid disease has been entered into clinical trials.

Questions and Answers

A participant expressed concern about the contamination of thyroid cell lines and indicated that more information on this issue would be published by his laboratory in the near future. He added that cell populations in PTC are implicitly heterogeneous and, consequently, are the metastasized lesions. It is therefore crucial for investigators to realize that what is analyzed in the laboratory may represent a mixture of populations. In response to this statement, Dr. Fagin agreed that tumor heterogeneity needs to be appropriately addressed and that primary genetic events need to be distinguished from those that occur subsequently.

Another participant expressed concern about the use of death as the only end point of disease and suggested that other types of outcomes (e.g., emotional, physical, quality of life) be considered, particularly with recurrent disease. Dr. Davies agreed and added that the SEER does not monitor functional outcomes such as recurrent disease. In turn, the participant recommended that the NCI dedicate resources to the creation of a database that would store such data for all cancers.

Yet another participant pointed out that the data presented by Dr. Davies in support of a subclinical disease reservoir do not rule out an alternate disease etiology; e.g., incidence of childhood thyroid cancer increased in the 1990s as a result of the Chernobyl disaster. He added that if tumors are small, point cause is not eliminated. Dr. Davies agreed that certain events may be contributing to an increase in thyroid cancer incidence. However, it is important to note that disease mortality is not changing, and surgeons are faced with the choice of performing surgery on a small lesion versus monitoring the patient.

In response to a query regarding mTOR kinase and associated downstream metabolism in thyroid tumors, Dr. Fagin answered that conditional activation of RET in a thyroid cell line by the Akt pathway moderately increases mTOR activity. The impact on metabolism remains to be analyzed.

A participant inquired about recommendations for investigators who work with cell lines and whether thyroid cell lines should be stored in a central repository. Dr. Haugen replied that the DNA profiling analysis conducted by his group was robust and is widely available. Many centers and companies can conduct such analyses. Investigators can send DNA to these centers and compare resulting profiles to the American Type Culture Collection (ATCC) databases or other known cell line databases to determine if any contamination is present. Dr. Fagin added that dissemination of cell lines by his laboratory has been discontinued. Also, he suggested that if the ATCC could store and distribute cell lines, it would greatly reduce the burden on investigators.

Another participant added that STR analysis as proposed above is not sufficient; the only true test is to conduct STR analysis on the originating tumor, maintain the STR pattern, and provide the STR pattern along with the cell line to other investigators so that the receiving laboratory is able to continuously test the cell line for genetic drift and contamination.

In response to a question on vascular invasion, Dr. Ringel replied that EMT data point to the existence of a relationship between vascular invasion and vimentin staining in the validation study. He also emphasized the importance of considering tumor heterogeneity and the fact that one metastatic lesion is not necessarily the same as another. Studying those tumors would be important in understanding the biology of aggressive disease.

A participant asked Dr. Davies whether the diagnosis of untreated thyroid cancer patients had been made just by fine needle aspiration (FNA) biopsy and added that obtaining a definitive diagnosis from an FNA is challenging. Dr. Davies agreed and added that registries at centers with the largest number of cases did not know how diagnosis of untreated patients was made. Part of the problem is related to communication between institutions; i.e., in some cases, patients were treated at an institution other than the one where the diagnosis was made.

Mechanisms of RET/PTC Rearrangement in Radiation-Induced Thyroid Cancer

Yuri E. Nikiforov, M.D., Ph.D., University of Pittsburgh

External (γ-radiation), treatment (x ray), and accidental exposure to RAIs are risk factors for thyroid cancer, and radiation doses in the 0.2 to 2 Gy range have a nearly linear risk for the development of thyroid cancer.[23] Oncogene activation in sporadic and radiation induced thyroid cancer (including RET/PTC, the neurotrophic tyrosine kinase receptor Ras, and BRAF) occurs by different mechanisms. For instance, RET/PTC is activated by a large-scale RT/PTC chromosomal rearrangement rather than a sporadic occurrence. BRAF activation occurs via two mechanisms: mostly by point mutation between nucleotide 7 to 99, resulting in a V600E mutation, but also by chromosomal rearrangement.[24,25] The dominant mutation mechanisms in sporadic thyroid tumors is point mutations, while radiation-induced tumors occur via chromosomal rearrangement.

To elucidate the mutation mechanisms in radiation-induced and sporadic thyroid tumors, experimental induction of RET/PTC was achieved by γ-radiation in the HTori-3 thyroid cell line.[26] Ionizing radiation dose correlated with RET/PTC1 and RET/PTC3 rearrangements in a nearly linear fashion. Data on human cell carcinomas also indicated that RET/PTC chromosomal rearrangement represents a genetic signature of a radiation-induced tumor.

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[23] Cardis E, Kesminiene A, Ivanov V, et al. Risk of Thyroid Cancer After Exposure to ^{131}I in Childhood. *J Natl Cancer Inst*. 2005;97:724-732.
[24] Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. *Nature*. 2002;417:949-954.
[25] Fusco A, Viglietto G, Santoro M. A new mechanism of BRAF activation in human thyroid papillary carcinomas. *J Clin Invest*. 2005;115:20-23.
[26] Caudill CM, Zhu Z, Ciampi R, et al. Dose-Dependent Generation of RET/PTC in Human Thyroid Cells after in Vitro Exposure to γ-Radiation: A Model of Carcinogenic Chromosomal Rearrangement Induced by Ionizing Radiation. *J Clin Endocrinol Metab*. 2005;90:2364-2369.

PTC is a multistep process involving RET/PTC and other intrachromosomal rearrangements. Specific types of fusions are seen consistently in thyroid cancer, in part due to chromosomal architecture. A potential reason for this may be explained by an interphase chromatin packaging model.[27] If two parts of a chromosome are in proximity to each other, they are predisposed to fusion and other types of chromosomal rearrangements. For example, RET and H4 genes located on chromosome 10 are distant from each other, but, as shown by confocal microscopy studies, the formation of a loop structure brings them close together to generate a RET/PTC1 rearrangement.[28] In addition, RET and ELE1 genes in RET/PTC3 rearrangement are close to each other in a large number of human thyroid cells.[29] Thus, chromatin folded in a helical arrangement predisposes to the generation of specific gene fusions. Chromosomal and nuclear architecture also predispose to specific recurrent chromosomal rearrangements after exposure to ionizing radiation by placing genes in close proximity to each other. These events are intrachromosomal rearrangement fusions rather than intrachromosomal translocations.

Several theories exist that explain chromosomal aberrations induced by radiation, but none have been fully confirmed. To do so, exposure to ionizing radiation was modeled using restriction enzymes and immunofluorescence for γH2AX histones. A single break in the DNA was sufficient for rearrangement by homologous recombination and rearrangements may also develop by a direct mechanism. PvuII and StuI induced double-stranded breaks that were close to each other, modeling cluster DNA damage, a genetic signature for radiation exposure. Only when breaks occurred close to each other did a RET/PTC rearrangement take place. Inhibition of ataxia telangiectasia mutated kinase, a major protein in the homologous recombination pathway, may confer a genetic predisposition toward malfunctioning of the DNA repair pathway and induce chromosome rearrangement; i.e., radiation-induced carcinogenesis. Currently, Dr. Nikiforov and collaborators are initiating a study involving children who were exposed to the Chernobyl fallout to identify genes that may be malfunctioning in the process of DNA repair after radiation exposure. SNP polymorphisms identified in an *in vitro* system will in turn help identify SNPs that predispose individuals to the generation of thyroid cancer.

Prognostic Significance of B-Raf Mutation in Thyroid Cancer

Michael M. Xing, M.D., Ph.D., The Johns Hopkins University

PTC is rarely fatal and therefore, clinicians focus on prevention and monitoring of disease recurrence. Recently, the T1799A BRAF mutation has been associated with PTC. A meta-analysis published in 2007 showed a significant correlation between BRAF mutations and extrathyroidal invasion, lymph node metastases, and advanced stages; i.e., stage III or IV cancer.[30] Furthermore, both univariate and multivariate analyses indicated that PTC patients

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[27] Yokota H, van den Engh G, Hearst JE, et al. Evidence for the organization of chromatin in megabase pair-sized loops arranged along a random walk path in the human G0/G1 interphase nucleus. *J Cell Biol*. 1995;130(6):1239-1249.

[28] Nikiforova MN, Stringer JR, Blough R, et al. Proximity of chromosomal loci that participate in radiation-induced rearrangements in human cells. *Science*. 2000;290:138-141.

[29] Gandhi M, Medvedovic M, Stringer JR, et al. Interphase chromosome folding determines spatial proximity of genes participating in carcinogenic RET/PTC rearrangements. *Oncogene*. 2006;25:2360-2366.

[30] Xing M. BRAF mutation in papillary thyroid cancer: pathogenic role, molecular bases, and clinical implications. *Endocr Rev*. 2007;28:742-762.

with this BRAF mutation have approximately a 25 percent incidence of recurrence, whereas those without the BRAF mutation have only a 10 percent chance. Results from a multicenter study indicated that when all the conventional clinicopathological risk factors and RAI treatments were included in logistic regression analysis, the T1799A BRAF mutation was significantly associated with PTC recurrence.[31]

Several factors may contribute to the association between the BRAF mutation and poorer clinical prognosis. The T1799A BRAF mutation has been correlated with loss of RAI avidity in PTC tumors, which could account, at least in part, for poorer clinical outcomes as PTC is often treated with RAI. The loss of avidity may be due to the silencing of several genes, including the thyroid iodine–handling genes TSHR, NIS, TPO, Tg, and Pendrin. The BRAF mutation has also been linked to overexpression of tumor-promoting molecules (specifically VEGF, metalloproteinases, NF-κB, and mesenchymal-epithelial transition factor) and could likely explain the reason for recurrence of PTC. BRAF has been associated with methylation of tumor suppressor genes, including tissue inhibitor of metalloproteinases-3; solute carrier family 5 (iodide transporter), member 8; death-associated protein kinase; and the RAR-β2 gene. Finally, BRAF has been associated with methylation of the DNA repair gene human mutL homolog 1. Methylation of tumor suppressor and DNA repair genes likely leads to attenuation of their ability to function properly, thus accounting in part for poorer clinical outcomes in PTC patients with the BRAF mutation.

In summary, the BRAF/MAP kinase pathway, through the T1799A BRAF mutation, plays an important role in PTC tumorigenesis and progression. Given the clinical ramifications of BRAF mutations, assessment of BRAF status via FNA biopsy prior to surgical intervention may help clinicians determine how aggressively to treat the disease.

A *Drosophila* Model of MEN2 and Medullary Thyroid Carcinoma

Ross L. Cagan, Ph.D., Mount Sinai School of Medicine

Drosophila melanogaster (fruit flies) form effective cancer models as they possess conserved epithelia, organs, and genes relevant to human tumorigenesis. Furthermore, the *D. melanogaster* models permit the study of a disease *in situ* under controlled conditions.

MTC in multiple endocrine neoplasia (MEN) 2B patients is caused by mutations in the RET proto-oncogene. RET mutations targeted to the fruit flies' eyes result in eye overgrowth, tumors, switches in cell fate, and confinement of cells to the G2 and M phases of the cell cycle. A genetic modifier screen of approximately one-third of the fly genome in this model identified 93 enhancer and 47 suppressors that mediate RET. These genes fall into several families, including Ras, c-Jun N-terminal kinases, and Src. Deletion mutations in two of the enhancers, TNIK and CHD3, have been identified in 100 and 50 percent, respectively, of the subset of MEN 2B patients with pheochromocytoma, indicating that these deletions are either susceptibility loci or biomarkers of disease.

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[31] Xing M, Westra WH, Tufano RP, et al. BRAF mutation predicts a poorer clinical prognosis for papillary thyroid cancer. *J Clin Endocrinol Metab*. 2005;90:6373-6379.

The *D. melanogaster* model is also useful for drug screening. Flies with known mutations were grown from embryo to adult in 96-well plates in the presence of therapeutic agents. Eye development and whole animal toxicity were then evaluated in the adults. Thirty-nine compounds with therapeutic potential were identified, including sorafenib, ZD6474, dasatinib, and SU6656. ZD6474—an inhibitor of VEGF, EGF, and RET receptor tyrosine kinase—held the most promise in that it enabled normal eye development with low toxicity. This compound has since been brought to phase III clinical trials. High-level sequencing is underway to identify mutations linked to drug resistance in humans. Testing of other drugs to counteract resistance will be conducted in a transgenic *D. melanogaster* model.

One of the modifiers identified during the above-mentioned genetic screen is Src. Src is linked to tumor metastasis and is negatively regulated by Csk. When Csk was knocked down in a patch of tissue in flies, endogenous Src was activated locally. Due to a cell boundary effect and interaction with epithelia, cells at the patch's edge migrated to form secondary tumors in a model of secondary metastasis. In a double *D. melanogaster* drug screening model, a hedgehog inhibitor similar to cyclopamine was identified that is effective in blocking this boundary effect. A syngeneic mouse model, generated via injection of 4T1 breast cancer cells into the left ventricle, resulted in tumor invasion of the lung, which could be blocked with cyclopamine. Investigations of which drugs influence the activity of specific intracellular proteins have led to the development of a model of the RET pathways involved in tumorigenesis and metastasis.

To inhibit tumor formation, an adult *D. melanogaster* tumorigenesis model was developed involving multiple oncogenes linked to a heat-sensitive promoter. When flies were placed on a warm platform, tumors would develop in their feet within days and metastasize to various tissues within a week. Investigations are ongoing regarding the tissue-specific oncogenes and tumor suppressor genes involved in metastasis. Taken together, the multigenic fly models have enabled researchers to address many aspects of MEN 2B tumors.

Questions and Answers

A participant commented that thyroid cancer is relatively unique compared to other cancers as there is a separation between metastatic lesions and tumor proliferation. As an example, some patients with lung metastases are stable, others with metastatic disease progress, and some who remain stable for many years suddenly progress. He asked whether it was possible to separate those processes in metastatic lesions by oncogenes, suppressors, or modifiers responsible for their regulation. Dr. Cagan replied in the affirmative. In the fly and human breast and lung tumors, almost all the activity observed in secondary metastases also takes place in primary tumor boundaries. There is clearly an interaction between the tissue being invaded and the invading cells. For example, as shown earlier, lung metastases are sensitive to cyclopamine, but bone metastases worsen. If lung cells are injected into bone accompanied by the drug, the cancer is eliminated. Otherwise, it remains insensitive to cyclopamine and grows aggressively.

A participant noted that there is mounting evidence that RET rearrangement is not solely caused by radiation and asked Dr. Nikiforov whether his laboratory had conducted any work in this area. Dr. Nikiforov stated that he and his colleagues believe that RET rearrangement can be induced by its location on fragile DNA sites such that RET is influenced as a result of exposure to various chemicals including caffeine and alcohol.

Another participant asked whether there is an influence of age on BRAF status and disease prognosis. Dr. Xing replied that, in many studies, evidence regarding the influence of age on BRAF mutation is unclear. However, in general, age does not seem to play an important role in BRAF mutation and disease prognosis.

A participant asked why some flies become resistant to treatment over time and metastasis still occurs. Dr. Cagan replied that flies do not live long enough to accumulate too many mutations. When multiple oncogenes are activated, metastasis occurs in only 80 percent of flies. Even if flies are treated with drugs, the drugs are not 100 percent efficacious; e.g., dasatinib is 60 to 70 percent efficacious. Other factors, such as differences in gene copy number, may come into play.

PLENARY SESSION II: EXPERIENCE FROM THE CHERNOBYL RESEARCH

MODERATOR: Geraldine Thomas, Ph.D., Imperial College London

Chernobyl and Thyroid Cancer

R. Michael Tuttle, M.D., Memorial Sloan-Kettering Cancer Center

Dr. Michael Tuttle reminded participants that on April 4, 1986, electricity to one of four of the Chernobyl complex nuclear reactor units was lost. Within 40 seconds, the accumulated heat and steam caused explosions and resultant fires, killing several people, destroying the reactor, and exposing the radioactive core. Radioactive fallout was propelled into the atmosphere, contaminating parts of Ukraine, Russia, Belarus, and Europe. Acute radiation sickness eventually killed 134 plant and emergency workers. A sarcophagus was built over the reactive core to contain the radiation. However, concerns about its continued integrity have led to proposals for a second containment unit to be built over the first.

As many as 5 million people were exposed to radioactive fallout, which included approximately 40 to 50 million curies of ^{131}I. The greatest human exposure to RAI resulted from drinking milk derived from cattle that had eaten contaminated grass. The thyroid gland concentrates iodine and the general iodine deficiency in affected regions led to greater uptake of RAI from the milk than would have otherwise been the case. The estimated dose consumed by evacuee children (from newborns to 7 years of age) was between 100 and 300 centigrays. The estimated adult dose was lower due to larger thyroid glands and reduced milk consumption.

Reports of unusually high rates of childhood thyroid cancer began to surface in Ukraine, Belarus, and Russia in the early 1990s. In 2000, the United Nations Scientific Committee on the Effects of Atomic Radiation reported 2,000 cases of childhood thyroid cancer between 1990 and 1998 in these countries. More recent studies reported nearly 5,000 individual cases, the majority in children who were younger than 14 years of age at the time of the accident.

Of 740 surgically treated childhood thyroid cancer cases in Belarus, 62.3 percent occurred in girls, and the mean age of treated patients was 11.7 years.[32] Of these children, 57.6 percent

[32] Demidchik YE, Demidchik EP, Reiners C, et al. Comprehensive clinical assessment of 740 cases of surgically treated thyroid cancer in children of Belarus. *Ann Surg*. 2006;243:525-532.

received complete thyroidectomies, and approximately 63 percent of the total also underwent RAI ablation. According to the tumor node metastasis staging system, 72.6 percent of these tumors fell into the T1 category; while 10.5, 16.2, and 0.4 percent fell into the T2, T3, and T4 categories, respectively. Lymph node status was negative (N0) for 30.4 percent of the cases, N1a for 30.7 percent, and N1b for 38.6 percent. At the time of surgery, significant percent of patients did not exhibit metastatic disease. However, 10.2 percent of patients presented with pulmonary metastases at the first posttherapy scan. At a mean follow-up of approximately 9.5 years after surgery, 27.6 percent of the cohort had experienced a local recurrence and/or distant metastasis. To date, 15 deaths have been attributed to Chernobyl-related thyroid cancers.

The biological behavior of Chernobyl-related PTC is similar to sporadic PTC in terms of recurrence rate, distant metastasis rate, and response to appropriate therapy. Follow-up data 10 to 15 years postsurgery indicate that these cases have a low disease-specific mortality rate in the short term. However, the full impact of the Chernobyl accident will only be known in many years.

Thyroid Cancer Following the Chernobyl Accident: An Overview of Research Activities and Findings

Scott Davis, Ph.D., Fred Hutchinson Cancer Research Center

Dr. Scott Davis began his presentation by discussing a study funded by the Office of Naval Research that included collaborative teams in Russia and the United States. The purpose of this study was to investigate whether the risk of thyroid cancer is greater among children who were exposed to radiation from the Chernobyl power station accident than in nonexposed children. Sixty-six participants (38 females, 28 males) were identified from the Bryansk Cancer Registry and enrolled in the study. To qualify, research participants must have been (1) diagnosed prior to October 1997, (2) 20 years old or younger at the time of the accident, and (3) present in 1 of the 8 most contaminated raions (administrative districts akin to counties). All thyroid cancer cases in the study were independently diagnosed and confirmed. Two control individuals per cancer patient were enrolled, matched to birth year, gender, raion, and type of settlement. The study was later expanded to include cases fitting the same criteria from the entire Bryansk oblast (administrative division akin to a province or state) and diagnosed through August 1998.

Data collection tools included a dosimetry questionnaire and a medical and family history interview. A review of medical records also was conducted for each participant. This was the first study to estimate individual radiation doses, which was achieved using a computer model and information regarding thyroid RAI measurements, local environmental contamination, physical samples from the home and yard, and the results of the dosimetry questionnaire regarding milk and food consumption. Although the study was based on a small sample size, the results indicated a large and significant increase in the risk of thyroid cancer—primarily papillary—associated with radiation dose. This was consistent with descriptive and ecologic studies and a case-control study in Belarus.

A second ongoing study focuses on the examination of molecular changes associated with thyroid cancer risk after the Chernobyl accident. This study has three primary purposes: To investigate whether specific markers of genetic changes are associated with individual radiation dose, whether age-at-exposure–dependent radiation dose response differs according to presence

or absence of molecular markers, and whether molecular markers are associated with clinical outcome. Cases and controls are recruited, and individual radiation doses are estimated in the same manner as the previous study. This population-based study focuses on individuals who were between 0 and 50 years old at the time of exposure, including 252 cases and 252 controls, with 203 females and 49 males per group. Based on preliminary analyses, thyroid cancer risk appears to be similar for males and females and for all ages at exposure. Thyroid tissue remains to be evaluated for tyrosine kinase expression, RET/PTC mutations, and gene amplification.

Pathology of Pediatric Thyroid Cancer: Lessons Learned From Chernobyl

Virginia LiVolsi, M.D., University of Pennsylvania

Prior to the Chernobyl accident, sporadic pediatric PTC was extremely unusual in children under 10 years of age. Pediatric PTC includes several pathological types: Classic PTC, a follicular variant, a solid variant, and a diffuse sclerosing variant (DSV). PTCs and other thyroid carcinomas are defined by their distinctive nuclei, which tend to be enlarged and oval, with central clearing, a thick nuclear membrane, intranuclear grooves, intranuclear cytoplasmic inclusions, and small nucleoli adjacent to the nuclear membrane.

PTCs comprise 94.5 percent of post-Chernobyl thyroid tumors and, like sporadic pediatric PTCs, have excellent prognoses. The pathological features of classic PTC—11 percent of post-Chernobyl PTCs—include the presence of papillae, follicles, and psammoma bodies; multifocal and bilateral lesions; and regional lymph node metastases. Follicular variants of PTC—36 percent of post-Chernobyl PTCs—rarely contain psammoma bodies; have fewer lymph node metastases, less multifocality, and greater vascular invasion; and form a heterogeneous group, including infiltrative, encapsulated invasive, and encapsulated noninvasive tumors.[33] The solid variant of PTC, poorly described prior to the Chernobyl accident and comprising 32 percent of post-Chernobyl PTC cases, appears less differentiated and displays frequent lymph node metastases and extrathyroidal and vascular invasion, minimal thyroglobulin production, and mitotic activity. Six percent of post-Chernobyl PTCs are DSV, and 15 percent are mixtures of more than one variant. Tumors of uncertain malignant potential also have been identified in post-Chernobyl patients. For clinical purposes, these are considered follicular carcinomas and are treated conservatively until more is known about them.

The tumor latent period in post-Chernobyl PTCs correlates with tumor morphology and aggressiveness.[34] Tumors with a short latency tend to be solid and include extrathyroidal invasions. In contrast, those with long latencies are more likely to be the classic papillary and follicular variants and display a lower degree of invasiveness. Compared with PTCs in the United Kingdom and Japan, tumors from Chernobyl patients were the least differentiated and more likely to be solid. This may be due to high levels of dietary iodine in Japan and

[33] Liu J, Singh B, Talini G, et al. Follicular variant of papillary thyroid carcinoma: a clinicopathologic study of a problematic entity. *Cancer*. 2006;107:1255-1264.

[34] Williams ED, Abrosimov A, Bogdanova T, et al. Thyroid carcinoma after Chernobyl latent period, morphology and aggressiveness. *Br J Cancer*. 2004;90:2219-2224.

intermediate levels in the United Kingdom compared to the moderate iodine deficiency seen in the Chernobyl region.[35]

Array CGH Profiles in Post-Chernobyl Thyroid Cancer

Horst Zitzelsberger, Helmholtz Zentrum München, Institute of Molecular Radiation Biology

Dr. Horst Zitzelsberger discussed studies undertaken by GENRISK-T, a consortium composed of thyroid cancer experts with experience in a variety of fields, to identify the genetic risk factors for thyroid tumors in mouse models and humans. The human studies involved comparisons of genomic and expression profiles between sporadic and radiation-induced papillary thyroid tumors. To this end, PTC biospecimens from the CTB were case-matched for age at diagnosis and oblast of residence but differed in exposure to Chernobyl fallout and radiation dose.

Interphase fluorescence *in situ* hybridization analysis of RET/PTC rearrangements indicated a distinct genetic heterogeneity in a subgroup of tumors, as did differential RT-PCR amplification of the extracellular and tyrosine-kinase domains of the RET gene. To address whether there are RET/PTC gene–associated aberration patterns in PTCs, gene copy number analyses were performed with bacterial artificial chromosome (BAC) array comparative genomic hybridization (CGH). Hierarchical cluster analysis of BAC array CGH data from a mixed PTC cohort (including post-Chernobyl PTC patients and PTC patients who were not exposed to Chernobyl fallout) discriminated between two tumor subgroups according to age and RET/PTC gene status. Hierarchical cluster analysis and principal component analysis of BAC array CGH data from an exclusively post-Chernobyl cohort discriminated three tumor subgroups based on RET/PTC gene status and tumor size. Specific aberration signatures were identified for particular tumor groups, including adult RET/PTC-positive cases, childhood RET/PTC-positive cases, RET/PTC-negative cases, and tumors of different size and metastatic potential. The variable genetic aberration patterns in RET/PTC-positive and -negative cases indicated different mechanisms of tumor development. No correlations were observed between genetic aberrations and radiation exposure history or histological tumor subtype.

BAC array CGH results from the mixed cohort, evaluated with Ensembl data mining, identified 46 novel genes that may be involved in thyroid carcinogenesis, including genes in the PI3K/Akt, apoptosis, interleukin-27, and angiopoietin receptor pathways. Some were specific to tumor subgroups, while others were found in commonly altered regions. Analysis of the post-Chernobyl cohort identified 21 candidate genes in cluster-specific altered regions and 53 candidate genes in commonly altered regions. Twelve genes were consistently detected in both tumor cohorts, including FOXO1A, SLITRK5, RB1, and PTEN, which are new candidate genes for thyroid tumorigenesis. Future work will focus on the involvement and interaction of new candidate genes and the associated pathways in thyroid tumorigenesis.

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[35] Williams ED, Abrosimov A, Bogdanova T, et al. Morphologic Characteristics of Chernobyl-Related Childhood Papillary Thyroid Carcinomas Are Independent of Radiation Exposure but Vary With Iodine Intake. *Thyroid*. 2008;18:847-852.

Questions and Answers

A participant clarified that the epidemiological results suggest that children have no greater tendency toward developing thyroid cancer after radiation exposure than adults and that the greater number of post-Chernobyl thyroid cancer cases in children was solely due to differing radiation exposure. Dr. Scott Davis agreed with this statement and added the caveat that the results he presented are preliminary and still being analyzed. He also recognized that these findings counter commonly held beliefs regarding age-of-exposure effects. The same meeting participant then asked whether the results suggest that radiation exposure does not cause genetic aberrations or differences in thyroid tumor pathology but causes disease recurrence. Dr. Thomas replied that the evidence points to an increased frequency of thyroid cancer in the population exposed to Chernobyl radiation fallout but no differences in phenotype or pathological presentation of sporadic thyroid cancer. Dr. Scott Davis added that descriptive registry data are consistent with an age-independent dose effect.

Another participant asked whether genes other than RET/PTC had been evaluated. Dr. Zitzelsberger and Dr. Thomas answered that BRAF and other genes evaluated to date did not distinguish tumor subgroups.

A third participant asked about the rationale for the GENRISK-T consortium to investigate mouse models of radiation-induced tumors. Because most genetic defects associated with human thyroid cancers are related to chromosomal recombinations that alter the position of genes, a mouse tumor cannot be expected to resemble or be associated with the same genetic alterations as the human disease. Dr. Thomas added that the project in question evaluated whether different genetic strains of mice were differentially predisposed to develop thyroid tumors following RAI exposure, which might enable identification of SNPs associated with tumor risk and thus help identify genes to evaluate in humans. She added that some mice in the study developed solid tumors similar to those seen in some post-Chernobyl patients. Another participant stated that his work on the RET gene in mice suggested that RET is not positioned on the chromosome in such a way as to recombine in a manner similar to human RET recombinations and that, in his opinion, the models would not be good models for radiation-induced tumorigenesis or RET/PTC rearrangements. Dr. Thomas agreed that, ideally, research should focus on human tissue.

In response to a query about whether siblings who developed post-Chernobyl PTCs exhibited similar tumor morphology, Dr. Scott Davis replied that the data with which he is familiar do not show any indication of similarities between siblings. Dr. Thomas added that the frequency of post-Chernobyl thyroid tumors in siblings was greater than chance would predict. However, it is difficult to parse the effects of genetic relationships from RAI exposure, which would be similar due to siblings living in proximity to one another.

Another participant expressed concern about the conclusion that RAI-induced PTC risk is not age dependent and urged researchers to continue to consider age-dependent risk a possibility. Dr. Thomas replied that the findings from the Russian study suggesting a lack of age dependency are not in line with studies from Belarus and Ukraine. Dr. Tuttle added that the study Dr. Scott Davis presented is the only one to evaluate individual radiation doses; all other studies estimate dosages for population groups. This opens the possibility that in large groups, the risk of developing PTC is higher in children, but evaluations of individuals might reveal different risk

levels depending on individual repair mechanisms and genetics. The question to address is whether there is an age-related difference in susceptibility to radiation-induced PTC. The preponderance of external beam radiation studies indicate that the risk of tumorigenesis decreases with increased age at exposure. Another audience member referred participants to the results from a study of post-Chernobyl Ukraine that would be presented by Dr. Maureen Hatch later in the program that suggest a strong age dependency in risk of developing RAI-induced PTC.

The Chernobyl Tissue Bank: Integrating Research on Radiation-Induced Thyroid Cancer

Geraldine Thomas, Ph.D., Imperial College London

The incidence of thyroid cancer in children is typically very low—0.5 to 1.5 per million per year. However, by 1990, it became apparent that the rate was abnormally high in oblasts affected by the Chernobyl fallout. The CTB was formed in 1998, with support from the European Commission, the NCI, the Sasakawa Memorial Health Foundation, and the Governments of Russia, Ukraine, and Belarus (currently suspended) to gather tissue and blood biospecimens from patients with thyroid cancer or cellular thyroid adenoma in affected areas. Over 2,900 biospecimens have been collected to date.

The CTB was established to create a central pool of information on the molecular changes associated with disregulated thyroid cell growth and thus provide insight into the process of thyroid carcinogenesis. The CTB employs standard operating procedures in biospecimen collection and postacquisition molecular assays to ensure the accuracy of the pathological diagnoses and the quality of the biospecimens, which in turn facilitate the generation of high-quality research data. Researchers are encouraged to access the bank for these reasons and because the bank addresses issues of informed consent;[36] enables high-throughput methods to screen large numbers of samples; and facilitates the association of research results with clinical presentation, outcome, or response to therapy.

The project is coordinated from the Imperial College London in conjunction with the Institute of Endocrinology and Metabolism in Kiev, Ukraine, and the Medical Radiological Research Centre of the Russian Academy of Medical Science in Obninsk, Russia. It includes annual review by Ukrainian, Russian, American, and British institutional review boards/ethics committee. CTB governance includes numerous committees, centers, and groups in the participating nations. The CTB database contains information relating to pathological features of the tumors, quality assurance of biological material and coded patient data. A web-based system is nearing completion, which will allow researchers to view information on their samples, track applications on-line, store research results and provide resources for bioinformatics. The CTB does not practice cost recovery; approved researchers are asked only for the price of sample shipment. Future endeavors of the CTB include expansion of the bioinformatics system to integrate a greater variety of image and data types and enable data mining projects. The CTB is a

[36] The CTB obtains generic (enduring) informed consent from the research participant (if he or she is older than 18) or his or her parent or guardian if the participant is younger than 18. Participants have the right to withdraw from the study at any point and are made aware that biospecimens may be sent abroad for study.

paradigm for modern tissue banking and has served as a model for more wide-ranging collections, such as the Wales Cancer Bank.

The CTB supports several major research initiatives that employ a number of molecular biological techniques to study multiple samples from the same patient. Some of these have already returned intriguing conclusions: RET gene rearrangements more likely correlate with the pathological thyroid cancer subtype, which varies with age, than radiation dose; the BRAF mutation, while uncommon, is more prevalent in older cohorts; and preliminary array technology results have not shown a relationship between molecular biological changes in the tumor and radiation dose. Together, these results suggest that the molecular biology of thyroid cancer, as with cancers of other tissues, differs in young and adult patients.

High-Quality Biospecimens: The Road to Molecular Medicine

Carolyn Compton, M.D., Ph.D., National Cancer Institute

Dr. Carolyn Compton introduced the NCI Office of Biorepositories and Biospecimen Research (OBBR) as an office within the NCI dedicated to facilitating the translation of research into personalized medicine through promoting optimal handling of collected biospecimens for modern technological platforms. In translational research, the biospecimen is of primary importance and by defining the molecular characteristics of the host and the disease; it enables greater accuracy in classifying therapeutic targets as well as in predicting disease susceptibility and treatment efficacy.

The NCI comprises numerous team science efforts with a common goal: to transform the science of cancer and its treatment. The Cancer Genome Atlas (TCGA) pilot project, for example, is aimed at broad, deep examinations of the molecular basis of three types of cancer, the results of which will be made public. TCGA and other NCI initiatives depend upon high-quality biospecimens.

With the development of powerful new tools and the phenomenal rate of technological advancement come significant risks; the technological capacity now exists to produce low-quality data from low-quality analytes derived from low-quality biospecimens with unprecedented efficiency. The biospecimen research community, in particular, faces significant challenges from varying processes and procedures that compromise molecular research: methods of handling and storage can affect the physical or biological state of the biospecimen; biospecimen-associated data elements influence how much is known about the character of the specimen; clinical information determines what is known about the patient and, therefore, the biological context of the biospecimen; and legal, ethical, and policy restrictions dictate what the researcher may do with the biospecimen or the data.

A direct effect of the variability in biospecimen handling is exemplified by the clinical uncertainty currently associated with Her2/neu testing: variations in biospecimen fixation procedures have led to false-positive or false-negative results in 25 percent of breast cancer cases, resulting in an unacceptable number of patients who do not receive appropriate treatment. Poor biospecimen quality or handling also can lead to incorrect clinical diagnoses. Research results, too, may fall victim to low-quality biospecimens via the production of irreproducible results or the misidentification of artifacts as biomarkers.

The OBBR is taking a comprehensive approach to compile data-driven policies and procedures on which biorepositories may be built as the state of the science evolves. As a first step, the OBBR developed the *NCI Best Practices for Biospecimen Resources*, recommendations for technical, operational, and biosafety best practices; quality assurance and control programs; interoperable informatics; and ethical, legal, and policy issues. Through its Biospecimen Research Network, the OBBR is also helping to create and increase awareness of a scientific evidence base for optimal biospecimen procurement, processing, and stabilization. Finally, the OBBR is partnering with accreditation and professional bodies, such as the College of American Pathologists, to ensure that these standards are integrated into the clinical medicine enterprise. In short, the OBBR's purpose is to foster state-of-the-science, evidence-based processes that ensure the molecular integrity and clinical relevance of the human biospecimens used in cancer research and clinical medicine.

Questions and Answers

A participant commented that contamination of the cell lines has devastated the field of thyroid cancer research. He asked whether an NCI repository could establish thyroid cancer–derived cell lines. Dr. Compton replied that the NCI is beginning to address this need. Although the OBBR has decided to focus on human biospecimens before addressing animal models or cell lines, the same principles of quality control and quality assurance apply. In the absence of many of the complications associated with improving the overall quality of human specimens, establishing high-quality cell lines will be an easier problem to resolve.

Another participant asked how, aside from standardizing procurement, the OBBR recommends accounting for tissue complexity and heterogeneity during biospecimen validation. Dr. Compton responded that this will have to be addressed in a research question– and platform-dependent manner.

Dr. LiVolsi commented that improving prospective biospecimen procurement and handling will face several challenges, including clinicians and hospital administrators who are unwilling to change their routines and budgets for the benefit of the research community. By focusing on prospective collection of fresh-frozen biospecimens, the OBBR would be neglecting archival tissues available in paraffin blocks. Therefore, Dr. LiVolsi suggested that the OBBR also fund research that addresses questions such as the effects of differing formalin fixation times.
Dr. Compton agreed that a wealth of information is contained in formalin-fixed, paraffin-embedded (FFPE) tissue and clarified that one of the goals of the OBBR's research initiatives is to generate quality indicators for FFPE biospecimens. Dr. Thomas added that the onus is on researchers to develop such quality metrics. She mentioned a study by van Beers, et al in which multiplex PCR was employed to identify FFPE tissue adequate for array CGH (aCGH). Forty-three percent of archival FFPE tissues in that study were of sufficient quality for aCGH.[37] Dr. Thomas stated that her research group had performed a similar evaluation on archival breast cancer tissue and found that 85 percent of the archival tissue met the quality criteria; poststorage quality assurance is essential. Dr. Compton asserted that researchers have an ethical imperative

[37] van Beers EH, Joosse SA, Ligtenberg MJ, et al. A multiplex PCR predictor for aCGH success of FFPE samples. *Br J Cancer*. 2006;94(2):333-337.

to use archival tissue for scientific advantage because, unlike prospective collection, archival cases are accompanied by rich clinical data.

Summary of Plenary Sessions I and II

James A. Fagin, M.D., Memorial Sloan-Kettering Cancer Center

Dr. Fagin summarized presentations held during sessions I and II of this meeting. Session I described the epidemiology of sporadic thyroid cancer and the challenge it presents to clinicians. This first session also covered genetic abnormalities associated with thyroid cancer, how they affect prognosis, and how they may be used for therapeutic decision making. However, much remains to be learned about the association between genetics and thyroid cancer. Even in simple systems, such as thyroid cancer cell lines with specific genetic anomalies, it is difficult to know which genes are critical for viability. Session II presented the experience from the Chernobyl research. The discussion of the mechanisms behind radiation-induced thyroid cancer was illuminating; participants should keep in mind that while radiation may cause RET/PTC rearrangements—as evidenced by studies in both humans and cell lines and the information presented on chromosomal structure—other mechanisms may also lead to RET/PTC rearrangements. More work needs to be conducted in this area to elucidate why RET/PTC rearrangements are prevalent in children who were not exposed to high levels of radiation.

Session II also emphasized the value of high quality biospecimens and the CTB resource specimen collections. Researchers should consider utilizing the CTB banked biospecimens to address particular research questions. It is unclear how much of the post-Chernobyl thyroid cancer information generated so far will need to be revised due to uncertainties relating to the underlying materials, technical differences, and validation of the tumor specimens.

PLENARY SESSION III: TRANSLATIONAL APPROACHES IN THE TREATMENT OF THYROID CANCER

MODERATOR: Samuel Wells, M.D., Washington University

New Directions in Thyroid Cancer Treatment

Samuel Wells, M.D., Washington University

Dr. Samuel Wells discussed recent clinical trials of oral compounds in patients with medullary thyroid carcinoma (MTC). The standard response evaluation criteria in solid tumors (RECIST) have proven problematic in studies of molecular targeted therapeutics (MTT) in solid tumors, as the tumors grow slowly and the MTTs are cytostatic, not cytotoxic.

In a phase II trial of axitinib[38] in patients with all histologic types of thyroid carcinoma, there were 11 patients with MTC; 2 exhibited a partial response, 3 stable disease, and 6 had an indeterminant response. Clinical trials of gefitinib and imatinib showed minimal to no responses

[38] Cohen EE, Rosen LS, Vokes EE, et al. Axitinib is an Active Treatment for all Histologic Subtypes of Advanced Thyroid Cancer: Results from a Phase II Study. *J Clin Oncol*. 2008;26:4708-4713.

in patients with MTC[39,40]. In an open label study of motesanib diphosphate in 91 patients with advanced MTC, Schlumberger and associates reported a partial remission in 1% of patients and stable disease in 80%.[41] In a trial of sorafenib in five patients with advanced MTC, one patient went into complete remission and one into partial remission, indicating potential promise for this compound[42].

More recently, there have been studies evaluating larger number of patients with MTC. In a trial of vandetanib in 30 patients with MTC, approximately 20% of patients had an objective response.[43] In an ongoing trial of vandetanib in patients less than 18 years of age, the response rate thus far is similar to that in adults; however, only six patients are evaluable.[44] A third trial of vandetanib in patients with advanced hereditary and sporadic MTC has been completed; however, the data have not been completely analyzed and reported. Although levels of plasma calcitonin, a marker of MTC, are markedly decreased in most patients treated with vandetanib, this effect cannot be definitively attributed to tumor reduction, as there are data demonstrating that various tyrosine kinase inhibitors may directly inhibit the cellular secretion of this peptide.[45] Vandetanib side effects include nausea, diarrhea, and skin rash. Preliminary results of a trial of the tyrosine kinase inhibitor, XL184, in patients with advanced MTC have shown promising results. Approximately 53% of patients experienced a partial remission when treated with this compound. A current phase III trial of this compound in patients with advanced MTC is in progress.[46]

A major drawback to clinical trials such as those mentioned above is that researchers are rarely able to collect thyroid tissue from study participants, making the evaluation of molecular studies very difficult. There are a large number of studies of other MTT in patients with various types of thyroid cancer, the results of which represent an exciting advance in thyroid cancer.

Restoring Radioiodine Uptake in Thyroid Cancer

Kenneth B. Ain, M.D., University of Kentucky

Dr. Kenneth Ain opened his presentation by stating that, currently, the only effective pharmacotherapeutic agent for the treatment of non-medullary thyroid cancer is RAI. Tumoricidal activity requires at least 0.6 Gy per hour to be delivered to the thyroid and at least

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[39] Frank-Raue K, Fabel M, Delorme S, et al. Efficacy of imatinib mesylate in advanced medullary thyroid carcinoma. *Eur J Endocrinol.* 2007; 157:215-220.

[40] Pennell NA, Daniels GH, Haddad RI, et al. A phase II study of gefitinib in patients with advanced thyroid cancer. *Thyroid*. 2008;18:317-323.

[41] Malouf G, Baudin E, Soria JC, et al. Advances in the treatment of thyroid cancer in the era of molecularly targeted therapies. *Bull Cancer*. 2009 ;96(1):95-101.

[42] Kober F, Hermann M, Handler, et al. Effect of sorafenib in symptomatic metastatic medullary thyroid cancer. *J Clin Oncol (Meeting Abstracts)*. 2007;25:14065.

[43] Wells SA, Gosness RF, Ggel, et al. Vandetanib in metastatic hereditary medullary thyroid cancer: Follow-up results of an open-label phase II trial. *J Clin Oncol (Meeting Abstracts)*. 2007;25:6018.

[44] Fox BA, Baliss F, Wells S. Personal communication.

[45] Akeno-Stuart N, Croyle M, Knauf JA et al. The RET kinase inhibitor NVP-AST487 blocks growth and calcitonin gene expression through distinct mechanisms in medullary thyroid cancer cells. *Cancer Res*. 2007;67(14):6956-6964.

[46] Salgia RS, Sherman SI, Hong DS, et al. A phase I study of XL184l a RET, VEGFR2, and MET kinase inhibitor, in patients (pts) with advanced malignancies, including pts with medullary thyroid cancer (MTC). *J Clin Oncol (Meeting Abstracts)*. 2008; 26:3522.

80 Gy of RAI to be retained, which in turn requires a functional NIS. RAI treatment is ineffective for thyroid tumors that have lost the ability to absorb and retain iodine. One method to effectively target such tumors is through the restoration of iodine uptake.

The loss of iodine uptake may be caused by mutation, which is not easily reversible, or by posttranscriptional error or transcription failure for a reason other than mutation, both of which may be reversible by treatment with a pharmaceutical agent. Preliminary sequencing results of NIS in tumor specimens revealed no obvious mutations, but RT-PCR studies indicated a reduction in NIS messenger RNA (mRNA). Extensive methylation of the NIS promoter and the first NIS exon along with a closed chromatin structure were identified as possible causes of reduced transcription, leading to the hypothesis that reducing histone binding or polyamine synthesis may reinstate transcription. The DNA methylation inhibitor 5-azacytidine restored NIS mRNA expression in four of seven thyroid cancer cell lines as well as iodine uptake in two of these cell lines. However, a phase Ib clinical trial of 5-azacytidine failed to restore iodine uptake in thyroid tumors. Perhaps a longer trial would have yielded greater success because 5-azacytidine prevents methylation but does not actively demethylate DNA. Treatment of a thyroid tumor cell line with 5-azacytidine and sodium butyrate, a histone deacetylase inhibitor, resulted in significantly increased expression of NIS mRNA and increased activity of a NIS-promoter/luciferase-reporter construct. Addition of cycloheximide and other protein synthesis inhibitors amplified this effect.

Evaluation of mutant NIS promoter sequences transfected into thyroid tumor cell lines implicated poly (ADP-ribose) polymerase family, member 1 (PARP-1), in NIS repression. PARP-1 is a gene that encodes the chromatin-associated enzyme poly-ADP ribose polymerase-1. Treatment of a thyroid tumor cell line with a combination of 5-azacytidine, cycloheximide, and PJ34 (an inhibitor of PARP-1) resulted in a greater restoration of NIS mRNA expression than treatment with 5-azacytidine and cycloheximide. However, the best restoration effect was achieved with a treatment consisting of 5-azacytidine and sodium butyrate. Continuing work on the regulation of the NIS gene offers the promise of therapeutic agents that restore NIS expression and RAI uptake in thyroid cancer patients.

Nanoparticulate Tetrac Is Integrin-Targeted Therapy For Thyroid Cancers

Paul J. Davis, M.D., Ordway Research Institute

In vitro, thyroxine (T_4) and triiodothyronine (T_3) act at the integrin receptor to support tumor cell proliferation and angiogenesis in numerous cancers: thyroid, breast, glioma, head and neck, ovary, and pancreas. Tetrac, a potential nanotherapeutic agent produced by the deamination of T_4, has been shown to compete with and block the binding of both T_4 and T_3 to integrin $\alpha v\beta 3$, which bears the cell surface receptor for thyroid hormone. Within the cell, however, tetrac becomes thyromimetic, downregulating TSH production and leading to hyperthyroidism. Consequently, for tetrac to act therapeutically in preventing thyroid hormones from stimulating tumor growth, it may be necessary to prevent tetrac entry into the cell. Tetrac may be linked to the nanoparticle poly(lactic-co-glycolic acid) (PLGA) to create a thyroid hormone analogue that is capable of acting exclusively on the cell surface.

Both unbound tetrac and nanoparticulate tetrac have been shown to inhibit cell proliferation in FTC cell lines and to reduce tumor volume in MTC xenografts without having a significant

influence on host body weight. Tetrac also has been shown to block the proangiogenic action of T_4 and T_3 and to bear antiangiogenic qualities even in the absence of thyroid hormone. A toxicological evaluation of nanoparticulate tetrac soon will be initiated by a commercial laboratory.

In addition to tetrac's potential therapeutic value in inhibiting thyroid hormone agonist action at the receptor, therapy directed at integrin αvβ3 offers other potential advantages. Radiolabeled tetrac may be employed in nuclear scanning for tumor cells when NIS is lost. Tetrac also may be employed in radiosensitization of cancer cells. Additionally, nanoparticulate tetrac may be used to deliver other chemotherapeutic agents embedded in the nanoparticle.

MEK Inhibitors in Epithelial Thyroid Cancer

Barry D. Nelkin, Ph.D., The Johns Hopkins University

A number of studies suggest that Ras signaling pathway alterations—including mutations in the BRAF, RET/PTC, RAS, RAS association domain family 1A, and TRK genes—are preponderant in differentiated thyroid cancers.[47,48,49,50,51] Although BRAF mutations confer sensitivity to MEK inhibitors,[52] not all cell lines with RAS pathway mutations are necessarily sensitive to MEK inhibitors. Clinical trials of a number of MEK inhibitors have failed for various reasons. However, therapeutic potential is still under investigation for AZD6244, a potent, noncompetitive inhibitor of MEK1 and MEK2. Early preclinical data suggest that AZD6244 induces G_0/G_1 growth arrest in a variety of cancer cell lines and apoptosis in some melanoma lines with BRAF mutation. Results of a phase I trial suggest that it induces stable disease in a number of cancer types.[53] Several phase II trials of AZD6244, including one on differentiated thyroid carcinoma (DTC), are underway.

AZD6244 appears to inhibit MEK and arrest G_0/G_1 growth in putative thyroid cancer cell lines and inhibit tumor progression and ERK signaling in putative thyroid tumor xenografts. However, the questionable purity of the cell lines and xenografts employed casts doubt upon the

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[47] Kimura ET, Nikiforova MN, Zhu Z, et al. High prevalence of BRAF mutations in thyroid cancer: genetic evidence for constitutive activation of the RET/PTC-RAS-BRAF signaling pathway in papillary thyroid carcinoma. *Cancer Res*. 2003;63:1454-1457.

[48] Xing M, Cohen Y, Mambo E, et al. Early occurrence of RASSF1A hypermethylation and its mutual exclusion with BRAF mutation in thyroid tumorigenesis. *Cancer Res*. 2004;64:1664-1668.

[49] Nakamura N, Carney JA, Jin L, et al. RASSF1A and NORE1A methylation and BRAFV600E mutations in thyroid tumors. *Lab Invest*. 2005;85:1065-1075.

[50] Xing M. BRAF mutation in thyroid cancer. *Endocr Relat Cancer*. 2005;12:245-262.

[51] Nikiforov YE. Thyroid carcinoma: molecular pathways and therapeutic targets. *Mod Pathol*. 2008;21:S37-43.

[52] Solit DB, Garraway LA, Pratilas CA, et al. BRAF mutation predicts sensitivity to MEK inhibition. *Nature*. 2006;439:358-362.

[53] Adjei AA, Cohen RB, Franklin W, et al. Phase I pharmacokinetic and pharmacodynamic study of the oral, small-molecule mitogen-activated protein kinase kinase 1/2 inhibitor AZD6244 (ARRY-142886) in patients with advanced cancers. *J Clin Oncol*. 2008;26:2139-2146.

effectiveness of AZD6244 on thyroid cancer cells. The growth-inhibiting effect of AZD6244 has been linked with BRAF mutations in uncontaminated thyroid cancer cell lines.[54,55]

PI3K and mTOR are on a different branch of the RAS pathway than MEK and ERK. When MEK or ERK inhibitors were combined with PI3K or mTOR inhibitors, the combinations proved more effective against BRAF wild-type cell lines and xenografts than inhibitors of either branch alone. The effects included intense G_0/G_1 growth arrest, which resulted in cytostasis but not apoptosis. A phase I clinical trial of AZD6244 in combination with Torisel is in progress.

Taken together, these results suggest that specific mutations in thyroid cancer may predict treatment sensitivity and that combinations of specific signal transduction pathway inhibitors may be effective in treating thyroid cancer.

Translational Studies for Thyroid Cancer: Lessons Learned From Recent Clinical Trials

Manisha H. Shah, M.D., The Ohio State University Medical Center

Clinical trials are essential in identifying better therapies and enabling the advancement of anticancer treatments. Ideally, involvement in clinical trials should be an option for cancer patients. Conduct of a clinical trial includes selection of the drug to be tested; trial design; submission of the proposal to a governmental or industry sponsor; review by the U.S. Food and Drug Administration (FDA), sponsor, clinical scientific review committee, and institutional review board; accrual, treatment, and monitoring of the patients; and ongoing review and updates. An average of 1 year elapses between writing a clinical trial proposal and enrolling the first patient.

Clinical trials are particularly needed for thyroid cancer due to the lack of effective systemic therapy for metastatic MTC or iodine-refractory, metastatic DTCs and the generally poor results of multimodality treatment (i.e., chemotherapy, radiotherapy, and surgery) for ATC. Prior to 2003, few clinical trials had been conducted on thyroid cancer. Since then, 12 phase II clinical trials for thyroid cancer have been conducted. This has allayed researchers' concerns about adequate patient accrual and the availability of sponsors, but some concerns remain about cooperative support in the field, particularly with respect to international collaboration.

Several clinical trials of TKIs represent a breakthrough in treatment of iodine-refractory thyroid cancer, resulting in stable disease or partial response in a majority of participants.[56,57,58,59] These

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[54] Liu D, Xing M. Potent inhibition of thyroid cancer cells by the MEK inhibitor PD0325901 and its potentiation by suppression of the PI3K and NF-kappaB pathways. *Thyroid*. 2008;18:853-864.
[55] Leboeuf R, Baumgartner JE, Benezra M, et al. BRAFV600E mutation is associated with preferential sensitivity to mitogen-activated protein kinase kinase inhibition in thyroid cancer cell lines. *J Clin Endocrinol Metab*. 2008;93:2194-2201.
[56] Kloos, et al (manuscript in review).
[57] Gupta-Abramson V, Troxel AB, Nellore A, et al. Phase II Trial of Sorafenib in Advanced Thyroid Cancer. *J Clin Oncol*. 2008;26:4714-4719.
[58] Cohen EE, Rosen LS, Vokes EE, et al. Axitinib Is an Active Treatment for All Histologic Subtypes of Advanced Thyroid Cancer: Results From a Phase II Study. *J Clin Oncol*. 2008;26:4708-4713.

and other phase II trials of TKIs have demonstrated that therapeutic agents aimed at VEGF receptors are biologically and clinically active, that oral administration is relatively straightforward, and that these agents may have serious side effects. What remains to be learned about these therapies includes the optimal timing and dosing, the true target of the drugs, the mechanisms of primary and secondary resistance, the type of correlative studies to conduct, and ideal trial design and analysis. In summary, significant progress has been made to date, but further work in the field is needed.

Questions and Answers

A participant commented that TKI treatment may serve patients best in combination with ablative treatment. He also emphasized that researchers need to attend to the results of Gleevec trials in which initial dramatic responses lessened over time due to selective survival of tumor cells with mutations that blocked the drug's competitive action. Dr. Ain agreed, stating that the clinical trials for Gleevec were based on *in vitro* results using concentrations that were 100- to 1,000-fold higher than is achievable in humans. It is important to ensure that the preclinical results form a valid and sufficient basis for clinical testing before moving forward.

Another participant asked whether computed tomography scans have shown differential responses to TKIs in primary tumors and secondary metastases. Dr. Samuel Wells replied that he is not aware of any clinical trials on patients with primary tumors. Dr. Manisha Shah agreed that, generally, patients who are enrolled in clinical trials for thyroid cancer no longer exhibit primary tumors and are being treated for metastases, although anecdotal evidence suggests that TKIs are as effective in primary thyroid tumors as in metastases. Genotype evaluation of some thyroid cancer patients revealed the same mutations in primary tumors and metastases. Dr. Ain noted that primary and metastatic sites may have discordant responses.

Regarding the xenograft studies presented by Dr. Barry Nelkin, in which tumors that had been reduced with drug treatment regrew when treatment was withdrawn, Dr. LiVolsi asked whether the regrown tumors differed from the primary tumors. Dr. Nelkin replied that such differences were unlikely. An important study to perform would be to evaluate tumors that progress extensively during treatment. However, this is a rare occurrence and such a study has not yet been performed.

A participant asked whether the better response observed in vandetanib treatment of pediatric MEN 2B patients relative to vandetanib treatment of adult thyroid cancer patients is due to the age of the patients or the nature of the tumorigenic mutation. Dr. Wells replied that there was probably an age effect as no correlation was observed between genotype and response to therapy in the adult vandetanib trial. However, it may be premature to draw conclusions due to the small sample sizes in both the adult and the pediatric studies.

A participant asked what durable response rates to TKIs should be expected by a clinician; i.e., what is the best estimate of how many patients will have benefited from TKI treatment after 1

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[59] Sherman SI, Wirth LJ, Droz JP, et al. Motesanib diphosphate in progressive differentiated thyroid cancer. *N Engl J Med*. 2008;359:31-42.

year. Dr. Shah answered that in a clinical trial on 40 PTC patients with high tumor burdens, 40 percent of participants have benefited from the treatment for a year or longer.

Dr. Thomas commented that it is crucial to gain a better understanding of the biology of thyroid cancer, particularly primary tumors. Trials on patients with tumors expressing the receptor known to be the target of the therapeutic agent will have a better response rate. Dr. Wells agreed but pointed out that this is challenging for solid tumors.

Perspective From the Advocacy Community

Ms. Paula Kim, Translating Research Across Communities

Ms. Kim began by observing that significant work remains to be conducted in the field of thyroid cancer. Because thyroid cancer is a rare disease that is readily treatable, the voice of its patients and researchers often is not heard. Patient advocates may help address this by providing patient education, services, and support; advocating for public policy and funding; directing research funding; and representing the patient perspective on scientific committees. Patients look to advocates to assist with medical communication; facilitate access to clinical trial information and treatment; promote disease awareness; and provide information, support, and palliative care.

The formation of advocacy organizations has grown significantly in the past 2 decades based on the success of advocates for acquired immune deficiency syndrome, leukemia, breast cancer, and other forms of cancer. Advocates serve as translators for all stakeholders, including patients, researchers, and policymakers. Advocates are particularly helpful to researchers in improving patient participation in clinical trials by making clinical trial information available to potential research participants and educating patients about anonymization and other privacy issues.

Researchers could broaden the reach and depth of their role in translational medicine by partnering with advocates, reaping rewards such as greater awareness of their efforts and improved public trust. However, advancing cancer prevention and treatment most effectively will require scientists to share biospecimens and information and to collaborate more, fearing not what might happen if they do share and collaborate but what might *not* happen if they do *not*.

^{131}I Exposure From Chernobyl Fallout in Ukraine and Thyroid Disease 20 Years Later

Maureen Hatch, Ph.D., National Cancer Institute

Dr. Hatch informed participants that the study results she would be presenting remain to be published at the time of the conference. The study, which was conducted 20 years after the Chernobyl accident, focused on thyroid disease in individuals exposed to ^{131}I *in utero*. The fetal thyroid gland begins to develop at 12 to 13 weeks gestation and obtains iodine from the maternal circulation. For the study, 2,582 mother-child pairs were recruited. Mothers were pregnant at the time of or within 2 months of the accident. Of these pairs, 1,494 lived in regions contaminated with fallout and 1,088 were from areas considered uncontaminated. Direct thyroid RAI measurements were obtained for approximately half of the mothers; RAI dose for the rest was estimated as the median value for women in the same raion. Study participants were administered questionnaires regarding their pregnancy and medical histories, milk and vegetable consumption, and relocation. The cumulative RAI dose to the conceptus was extrapolated based

on the maternal dose and fetal age and included any postnatal exposure, which was generally low.

The average RAI dose in individuals from contaminated regions was 3.7 mGy in the first trimester, 104.2 mGy in the second trimester, and 232.2 mGy in the third trimester. Average exposures for the control group were 0.3, 7.0, and 19.2 mGy in the first, second, and third trimesters, respectively. Seven cases of thyroid cancer and one Hürthle cell neoplasm were identified. Of these eight cases, seven were from contaminated regions. Although the number of cases is few, the risk estimates, while non significant, are suggestive of radiation induction, reinforcing concern about exposure of pregnant women to RAI.

Two other genetic studies of thyroid cancer are being conducted in collaboration with the CTB and the Ukrainian-American Thyroid Study (Ukr-Am). The first aims to investigate genetic predisposition to radiation-induced PTC and involves candidate gene and genome-wide association studies approaches. The second is designed to evaluate a dose-dependent gene expression pattern in post-Chernobyl PTCs using RNA samples from Ukr-Am. Future endeavors will include additional projects with the CTB to investigate the duration of excess cancer risk, follow changes in histologic subtype, study the malignant potential of small nodules, and pursue the relative importance of latency and age at exposure in radiation risk. The post-Chernobyl cohort exposed *in utero* also will be revisited.

Questions and Answers

A participant suggested examining the pathogenesis of thyroid cancer in a cohort of individuals exposed to high levels of background radiation (from geological sources or radioactive cesium contamination as opposed to RAI) in areas of Chernobyl fallout. Dr. Hatch agreed that this would be an interesting undertaking.

PLENARY SESSION IV: THE FUTURE OF THYROID RESEARCH—PANEL DISCUSSION

MODERATORS: James A. Fagin, M.D., Memorial Sloan-Kettering Cancer Center; Geraldine Thomas, Ph.D., Imperial College London; Samuel Wells, M. D., MD Anderson Cancer Center

During this session, participants addressed the conference objectives of correlating research information gained from the studies of sporadic and Chernobyl-related thyroid cancer, identifying unexplored or underdeveloped areas in thyroid cancer science, and recommending future research directions to guide the DCB research priorities in coming years. Their recommendations and conclusions are summarized below.

Addressing the increase in thyroid cancer incidence. Several participants agreed that it will be critical to determine whether the incidence of thyroid cancer is increasing or whether the apparent increase is due to ascertainment bias. If the number of cases is on the rise, future endeavors should be aimed at identifying and investigating the causes of the increase in areas where radiation is not a factor. A user of the SEER database stated that age- and ethnic-adjusted information indicates an increase in regional and advanced-stage thyroid tumors. This is likely due in part, but not entirely, to improved disease detection. A 2002 review article addressed

possible environmental factors other than RAI that may contribute to thyroid cancer.[60] Participants suggested evaluating diagnostic radiology, obesity, pesticides, estrogen interrupters, and other dietary or reproductive factors. Bromates are another carcinogen to assess, KBr being the most reliable inducer of renal carcinoma in rats. Another research direction for understanding the etiology of the disease is to investigate what characterizes individuals who are most affected or are most likely to experience early recurrence of the disease.

Need for synergistic therapies. A participant emphasized the importance of considering synergistic therapies. TKIs, for example, may prove more effective in combination with other therapeutic agents, perhaps delivered via nanoparticles.

Utility of mouse models for preclinical investigation. Several participants encouraged funding agencies to recognize the utility of mouse models for preclinical investigations. However, some researchers are concerned that transgenic mouse models are patent protected and pharmaceutical companies are reluctant to allow their drugs to be tested in genetically modified mice. A mouse model is an excellent testing ground for drugs because the disease is in its natural microenvironment. A balance must be maintained, however, between studying mouse models and human tissue; transgenic mice are developed with known genetic mutations and therefore offer the opportunity to investigate therapies for known, but not for unknown, mutations.

Intracellular mechanisms of disease. Many participants recommended further molecular investigations into thyroid cancer. Elucidation of the genetics of the disease is critical; for example, half of MTC cases exhibit RET mutations, but the mutations behind the other half of MTC cases are unknown. Although the TCGA initiative is unlikely to map the genes involved in thyroid cancer in the near future, candidate genes will continue to emerge from other studies, which could lead to increased understanding of the pathway or pathways involved in thyroid cancer. It is also essential to further characterize the targets of therapeutic agents. Studies of intracellular disease mechanisms may be performed on metastatic biospecimens, although these are difficult to obtain for research because metastases are rarely removed surgically. Another method of obtaining human tumor cells is through the isolation of circulating tumor cells from blood. In addition to their utility for basic research, such cells, or cells obtained by biopsy, may be evaluated for gene signatures over time, enabling clinicians to assess whether different therapeutic agents are needed as the tumor evolves. Furthermore, little has been done to assess whether cancer initiation occurs in thyroid stem cells or differentiated cells that regress. Participants encouraged the NCI to match the funds the State of New York currently has available for stem cell research.

Host-tumor interrelationship. Several participants emphasized the importance of remembering that the patient is not simply a vessel for a tumor. Investigations of host-tumor interactions will be important to evaluate; for example, the reasons that lymph involvement in thyroid cancer is unlike lymph involvement in other cancers, why some therapeutic agents are ineffective in cell culture but work well *in vivo*, how the biology of thyroid cancer differs in young and old patients, whether active drug metabolites contribute to the efficacy of therapeutic agents, and why patients with metastases in different tissues have different prognoses.

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[60] Nagataki S, Nyström E. Epidemiology and primary prevention of thyroid cancer. *Thyroid*. 2002;12:889-896.

Integrating the thyroid research and medical oncology communities. A number of participants suggested that the thyroid research community may benefit from greater integration with the mainstream oncology and thus avoid relearning lessons learned by this community. An endocrine oncology fellowship would help foster such ties. Oncologists could benefit from a better understanding of endocrinology as well, particularly from recognizing that most PTC patients do well with minimal intervention; oncologists more familiar with other forms of cancer may be inclined to over treat thyroid cancer.

Clinical trial criteria. Several participants recommended reevaluating the entry criteria for clinical trials. Because 1 percent of clinical trial participants, on average, die as a result of the treatment, it is essential to choose patients for whom the risk is outweighed by the potential benefits. Patients with stable disease are inappropriate for inclusion in clinical trials for this reason and because stable disease is a desired end point of thyroid cancer trials. Therefore, a lack of change in such patients does not give any indication of the efficacy of the therapeutic agent being tested. A definitive set of prognostic criteria for trial inclusion needs to be identified.

RECIST criteria. A participant commented that the FDA Response Evaluation Criteria for Solid Tumors, also known as RECIST criteria, should be revised to include differential responses between primary tumors and metastases. This would allow a therapeutic agent not to be considered as a "treatment failure" when it leads to a stable disease in a distant metastasis, for example, even though it allowed disease progression at the primary tumor site.

NCI support of discovery research. Discovery research, which is by nature risky and yields uncertain results, is not normally covered by NIH R01 grants. Participants discussed other NCI support mechanisms. Several NIH committees have recently addressed issues of grant review with the intent of enabling more risk-prone research. Currently, such research might be conducted under R21 awards or Activity To Promote Research Collaboration, which is a mechanism that builds on R01 grants to generate novel cooperative efforts. The Small Business Innovation Research and the Small Business Technology Transfer programs are excellent mechanisms for funding academic-industry collaborations.

In conclusion, research into the biology of thyroid cancer has advanced greatly in recent years. However, as the incidence of thyroid cancer continues to increase, a significant amount of work remains to be done, with the ultimate goal of ensuring that patients receive optimal treatment.

MEETING CONCLUSION AND FUTURE STEPS

James A. Fagin, M.D., Memorial Sloan-Kettering Cancer Center

Rihab Yassin, Ph.D., National Cancer Institute

Drs. Fagin and Yassin thanked panel chairpersons, presenters, and participants for their participation in the meeting and the interactive discussions, which ensured the success of this conference, facilitated the establishment of collaborations, and the sharing of resources. Dr. Yassin also expressed her appreciation to the NCI DCB for recognizing the importance of the subject matter and supporting the conference. Dr. Yassin concluded by stating that a detailed meeting report will be generated for the benefit of the thyroid cancer research community and future initiatives in this field of science.

National Cancer Institute
National Institutes of Health
U.S. Department of Health and Human Services

THYROID CANCER STATE OF SCIENCE CONFERENCE: CHERNOBYL AND BEYOND

THURSDAY AND FRIDAY, 11-12 SEPTEMBER, 2008

MARRIOT BETHESDA NORTH HOTEL AND CONFRENCE CENTER
5701 MARINELLI ROAD
NORTH BETHESDA, MD 20852

Statement of the Meeting: This conference is convened to serve as the scientific platform for the review, dissemination and exchange of research information concerning thyroid cancer with the objective of advancing the understanding of the mechanisms underlying thyroid cancer formation, providing new avenues for treatment, and furthering collaboration between thyroid cancer scientists.

AGENDA

THURSDAY, 11 SEPTEMBER, 2008

7:00 A.M. – 8:00 A.M.	REGISTRATION
8:00 A.M.	**OPENING OF THE MEETING** ***BROOKSIDE ROOM***
8:00 – 8:05	NCI' Welcome *Dan Gallahan, Ph.D., National Cancer Institute*
8:05 – 8:15	Welcome and Presentation of the Meeting Objectives *Rihab Yassin, Ph.D., National Cancer Institute*
8:15 A.M. – 12:25 P.M.	**PLENARY SESSION I**
	THYROID CANCER STATE OF SCIENCE ***Moderator: James A. Fagin, M.D., Memorial Sloan Kettering Cancer Center***
8:15 – 9:00	Chair's Perspective: Thyroid Cancer Science-Where Does the Field Stand *James A. Fagin, M.D., Memorial Sloan Kettering Cancer Center*
9:00 – 9:25	Understanding the Rise in Thyroid Cancer Cases: Not as Simple as It Looks *Louise Davies, M.D., Dartmouth School of Medicine*
9:25 – 9:50	Mechanisms of Papillary Thyroid Cancer Invasion *Matthew D. Ringel, M.D., The Ohio State University*
9:50 – 10:15	Molecular-Based Therapeutics of Advanced Thyroid Cancer: Nuclear Hormone Receptors, Kinase Signaling and Cell Line Integrity *Bryan R. Haugen, M.D., University of Colorado*
10:15 – 10:35	Questions and Answers *All Presenters*
10:35 – 10:50	**COFFEE BREAK**

11 SEPTEMBER, 2008 (Continued)

10:50 – 11:15	Mechanisms of RET/PTC Rearrangement in Radiation-Induced Thyroid Cancer *Yuri E. Nikiforov, M.D., Ph.D., University of Pittsburgh*	
11:15 – 11:40	Prognostic Significance of B-Raf Mutation in Thyroid Cancer *Michael M. Xing, M.D., Ph.D., The John Hopkins University*	
11:40 – 12:05	A Drosophila Model of MEN2 and Medullary Thyroid Carcinoma *Ross L. Cagan, Ph.D., Mount Sinai School of Medicine*	
12:05 – 12:25	Questions and Answers *All Presenters*	
12:25 P.M. – 1:30 P.M.	**LUNCH BREAK**	***HOTEL RESTURAUNT***
1:30 P.M. – 5:15 P.M.	**PLENARY SESSION II**	***BROOKSIDE ROOM***
	EXPERIECE FROM THE CHERNOBYL RESEARCH ***Moderator: Geraldine Thomas, Ph.D., Imperial College London***	
1:30 – 1:55	Chernobyl and Thyroid Cancer *R. Michael Tuttle, M.D., Memorial Sloan Kettering Cancer Center*	
1:55 – 2:20	Thyroid Cancer Following the Chernobyl Accident: An Overview of Research Activities and Findings *Scott Davis, Ph.D., Fred Hutchinson Cancer Research Center*	
2:20 – 2:45	Pathology of Pediatric Thyroid Cancer: Lessons from Chernobyl *Virginia Livolsi, M.D., University of Pennsylvania*	
2:45 – 3:10	Array CGH Profiles in Post-Chernobyl Thyroid Cancer *Horst Zitzelsberger, Helmholtz Center Munich–Institute of Molecular Radiation Biology*	
3:10 – 3:30	Questions and Answers *All Presenters*	
3:30 – 3:45	**COFFEE BREAK**	
3:45 – 4:15	The Chernobyl Tissue Bank: Integrating Research on Radiation Induce Thyroid Cancer *Geraldine Thomas, Ph.D., Imperial College London*	
4:15 – 4:45	High Quality Biospecimens: The Road to Molecular Medicine *Carolyn Compton, M.D., Ph.D., National Cancer Institute*	
4:45 – 5:00	Questions and Answers *All Presenters*	
5:00 – 5:15	Summary of Plenary Sessions I and II *James A. Fagin, M.D., Memorial Sloan Kettering Cancer Center* *Geraldine Thomas, Ph.D., Imperial College London*	
5:15 P.M.	**ADJOURN FOR THE DAY**	

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AGENDA

FRIDAY, 12 SEPTEMBER, 2008

8:00 A.M. – 10:25 A.M.	**PLENARY SESSION III**	***BROOKSIDE ROOM***
	TRANSLATIONAL APPROACHES IN THE TREATMENT OF THYROID CANCER ***Moderator: Steven I. Sherman, M.D., MD Anderson Cancer Center***	
8:00 – 8:25	New Directions in Thyroid Cancer Treatment *Samuel Wells, M.D., Washington University*	
8:25 – 8:50	Restoring Radioiodine Uptake in Thyroid Cancer *Kenneth B. Ain, M.D., University of Kentucky*	
8:50 – 9:15	Nanoparticulate Tetrac is Integrin-Targeted Therapy For Thyroid Cancers. *Paul J. Davis, M.D., Ordway Research Institute*	
9:15 – 9:40	MEK Inhibitors in Epithelial Thyroid Cancer *Barry D. Nelkin, Ph.D., The Johns Hopkins University*	
9:40 – 10:05	Translational Studies for Thyroid Cancer: Lessons Learned from Recent Clinical Trials *Steven I. Sherman, M.D., MD Anderson Cancer Center*	
10:05 – 10:25	Questions and Answers *All Presenters*	
10:25 A.M. – 10:40 A.M.	**COFFEE BREAK**	
10:40 – 11:00	Perspective from the Advocacy Community *Ms. Paula Kim, Translating Research Across Communities*	
11:00 – 11:20	1^{-131} Exposure from Chernobyl Fallout in Ukraine and Thyroid Disease Twenty Years Later (Rescheduled from Day I) *Maureen Hatch, Ph.D., National Cancer Institute*	
11:20 – 11:30	Questions and Answers *All Presenters*	

12 SEPTEMBER, 2008 (Continued)

11:30 A.M. – 12:50 P.M.	**PLENARY SESSION IV**	***BROOKSIDE ROOM***
	THE FUTURE OF THYROID RESEARCH **PANEL DISCUSSION** **Moderators:** *James A. Fagin, M.D., Memorial Sloan Kettering Cancer Center, Geraldine Thomas, Ph.D., Imperial College London, Steven I. Sherman, M.D., MD Anderson Cancer Center, and Others* This session will address specific question provided to participants at the meeting	
12:50 P.M. – 1:00 P.M.	Meeting Conclusion and Future Steps *James A. Fagin, M.D., Memorial Sloan Kettering Cancer Center* *Rihab Yassin, Ph.D., National Cancer Institute*	
1:00 P.M.	ADJOURNMENT	