Recent Developments and Future Challenges in Thyroidology

Basic Review

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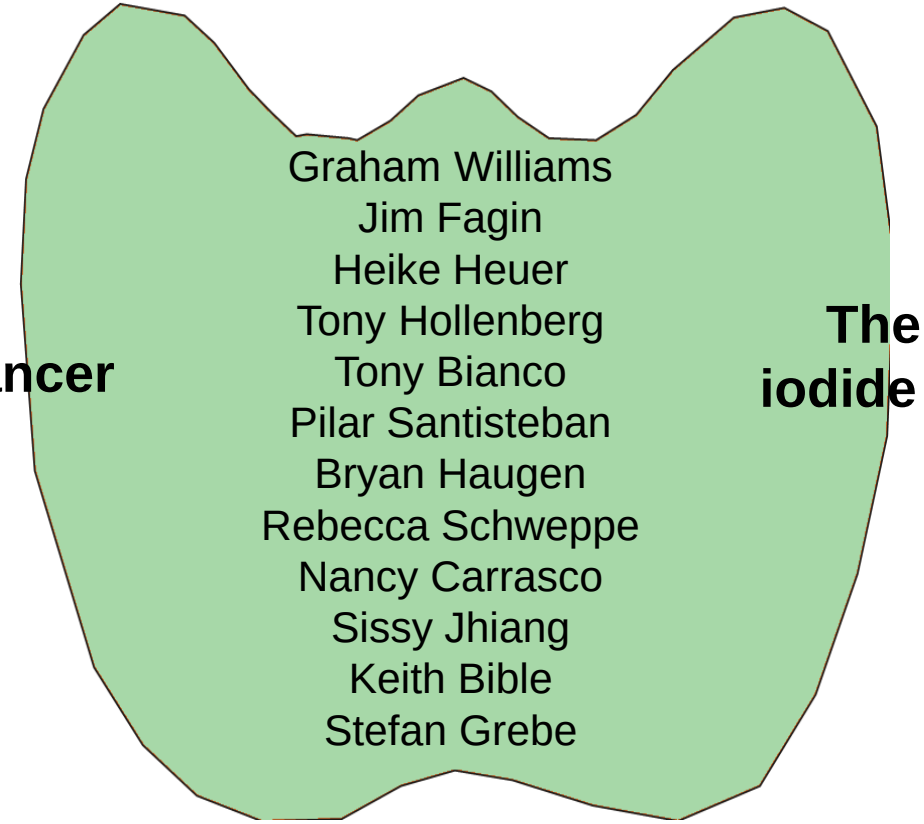
ATA Founded 1923

Disclosures

Nothing to disclose

Thyroid hormone & Aging
Thyroid hormone & Food Intake

Thyroid cancer



The sodium iodide symporter NIS

Non-classical thyroid hormone action
Novel thyroid hormone targets

Thyroid hormone & Aging

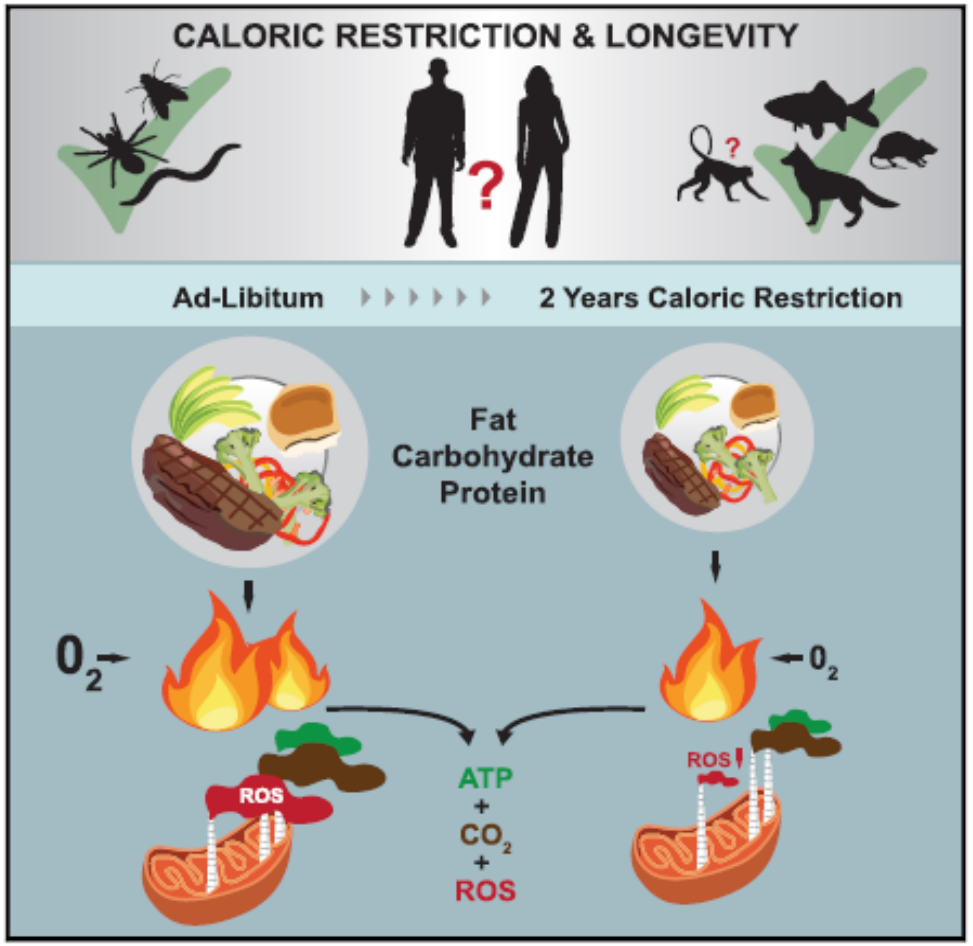
Thyroid hormone & Food Intake

Clinical and Translational Report

Cell Metabolism

Metabolic Slowing and Reduced Oxidative Damage with Sustained Caloric Restriction Support the Rate of Living and Oxidative Damage Theories of Aging

Graphical Abstract



Authors

Leanne M. Redman, Steven R. Smith, Jeffrey H. Burton, Corby K. Martin, Dora Il'yasova, Eric Ravussin

Correspondence

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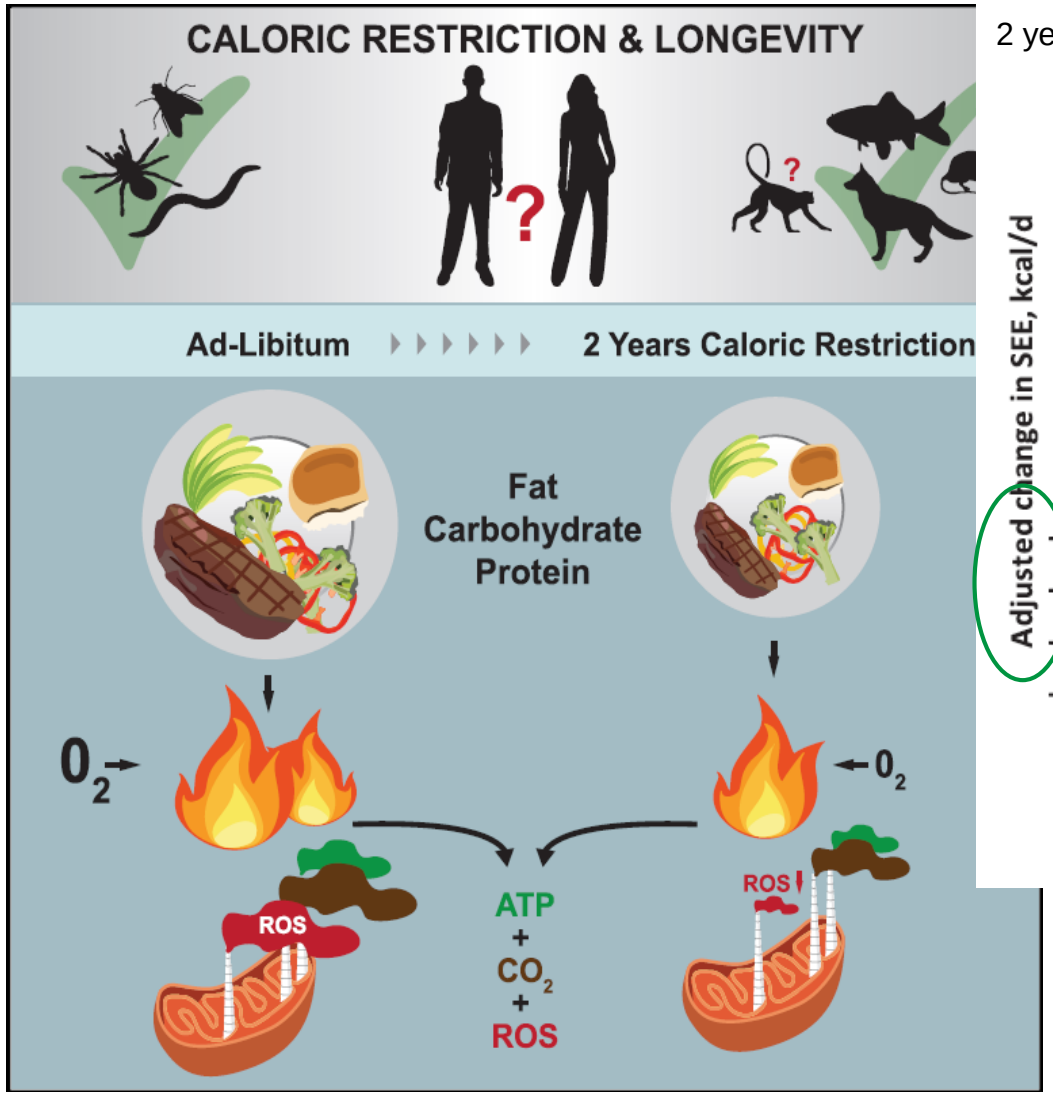
In Brief

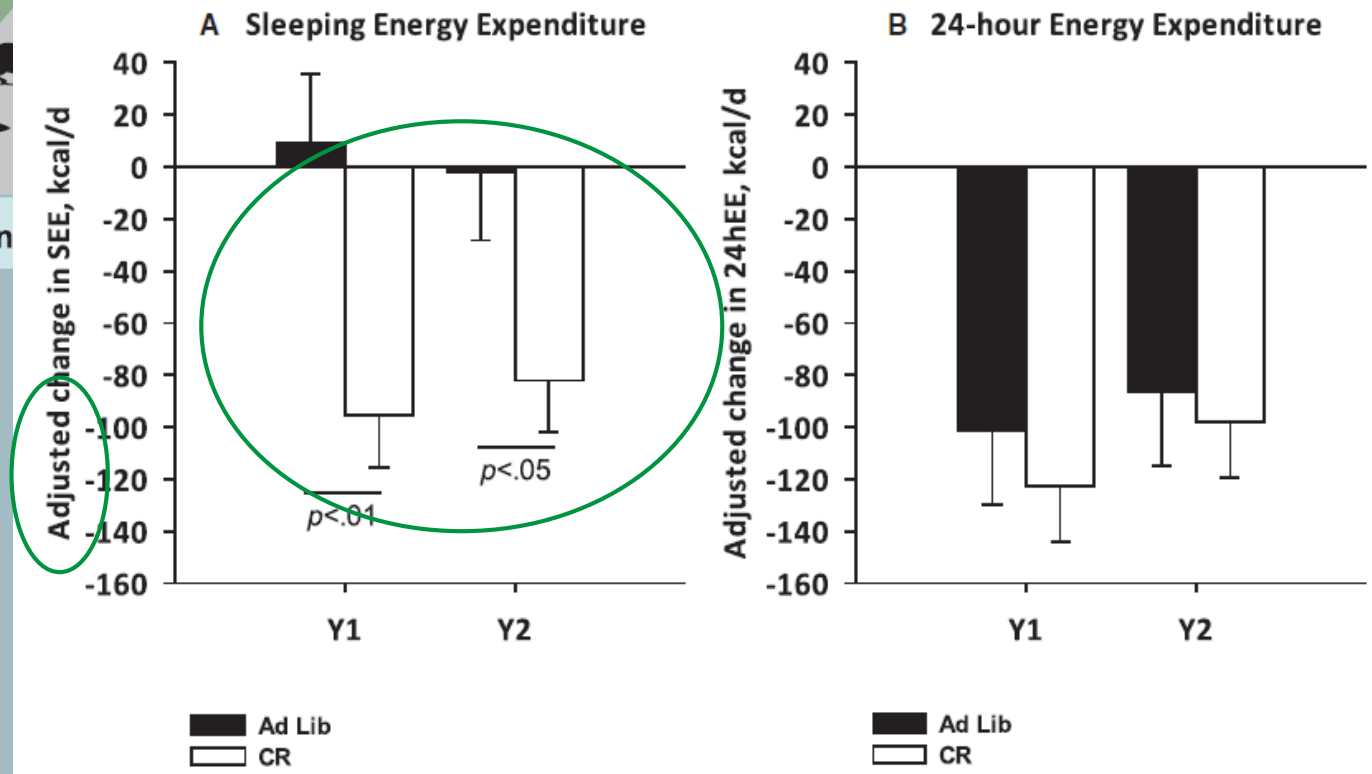
Calorie restriction (CR) has been shown to have health benefits and to extend lifespan in diverse species. Redman et al. conducted a 2-year CR trial in healthy, non-obese humans and found evidence that prolonged CR enhances resting energy efficiency, resulting in decreased systemic oxidative damage.

Redman LM, *et al.*, Cell Metabolism 2018; 27:805-815

Thyroid hormone & Caloric Restriction



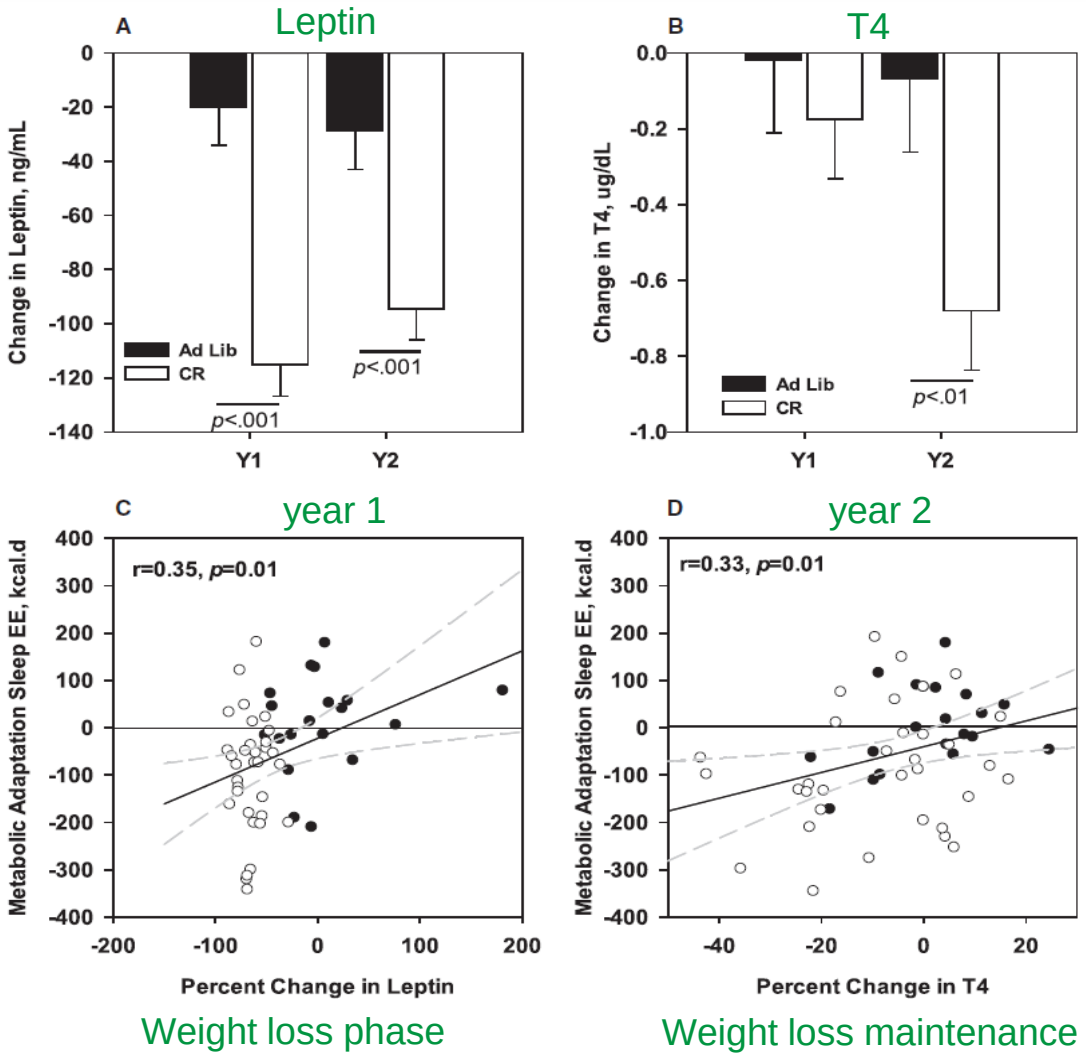
2 year calorie restriction trial: Healthy non-obese humans, CR n=34, controls n=19



➡ Sustained metabolic adaptation

Redman LM, *et al.*, Cell Metabolism 2018; 27:805-815

Thyroid hormone & Caloric Restriction



Weight loss phase

Weight loss maintenance

- Reduction in thyroid axis activity is a hallmark feature of the hypometabolic state with weight loss
- Drivers for maintaining metabolic adaptation or a consequence?
- Growing evidence that mechanisms of CR underlying increased life span work significantly through modulation of thyroid axis

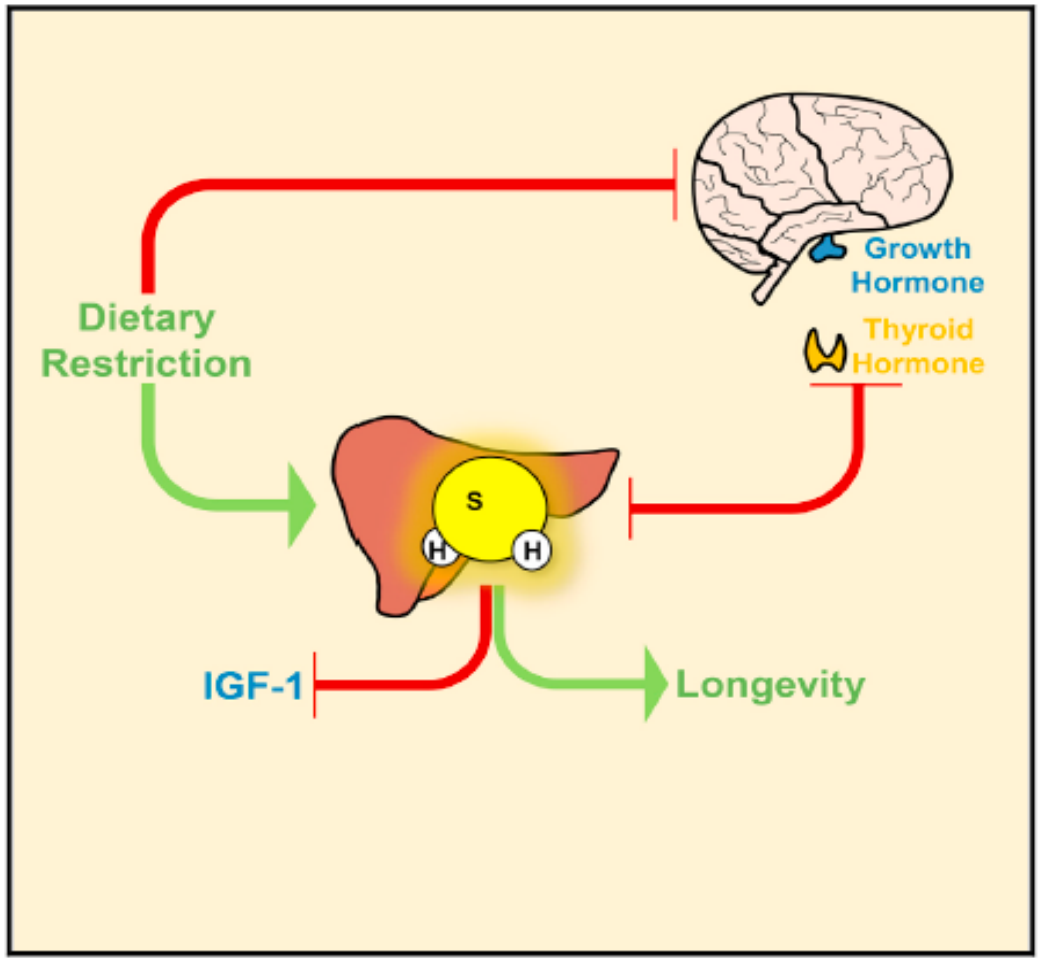
Redman LM, *et al.*, Cell Metabolism 2018; 27:805-815

Article

Cell Metabolism

Hypothalamic-Pituitary Axis Regulates Hydrogen Sulfide Production

Graphical Abstract



Authors

Christopher Hine, Hyo-Jeong Kim, Yan Zhu, ..., Richard Miller, Anthony N. Hollenberg, James R. Mitchell

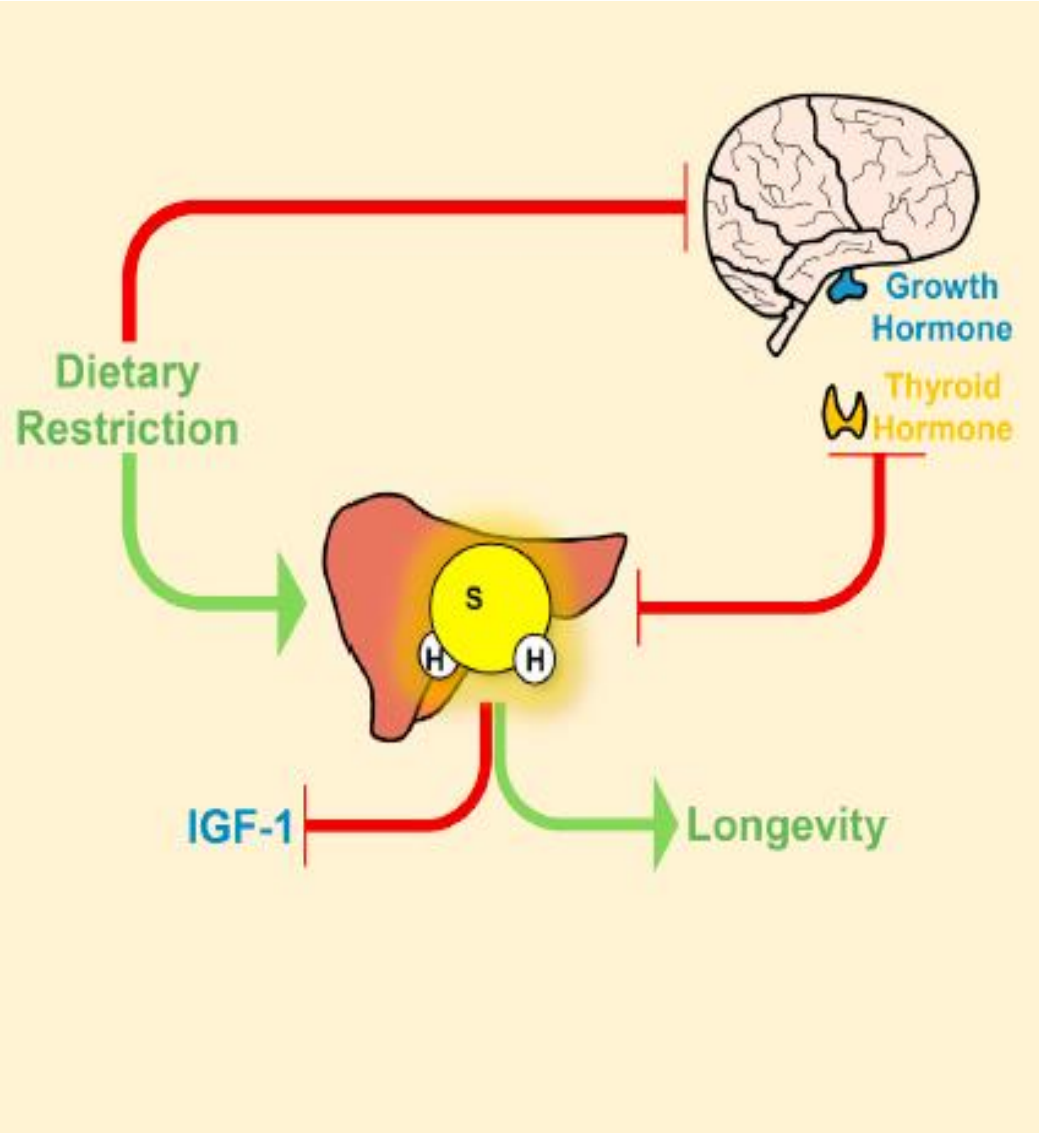
Correspondence

thollenb@bidmc.harvard.edu (A.N.H.), jmitchel@hsph.harvard.edu (J.R.M.)

In Brief

Reduced thyroid hormone (TH) and growth hormone (GH) activity are hallmarks of genetic models of longevity in mice. Here, Hine et al. find that TH and GH negatively regulate hepatic production of the longevity-associated gas hydrogen sulfide, which feeds back to negatively regulate circulating TH and IGF-1 levels.

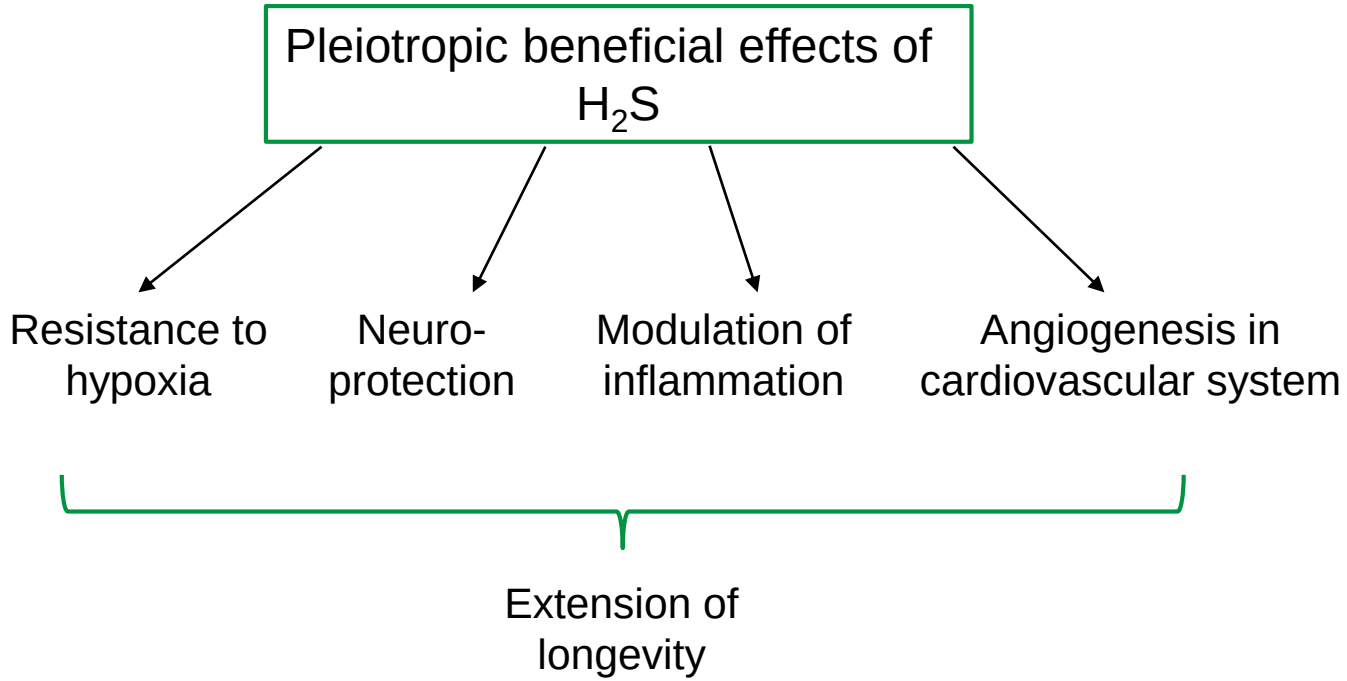
Thyroid hormone & hepatic H_2S production



- Decreased thyroid hormone and growth hormone signaling are associated with longevity and metabolic fitness
- Possible overlapping mechanisms with those of dietary restriction resulting in downregulation of TH/GH axis
- Potential mediator is the longevity-associated gas H_2S, which is increased upon dietary restriction

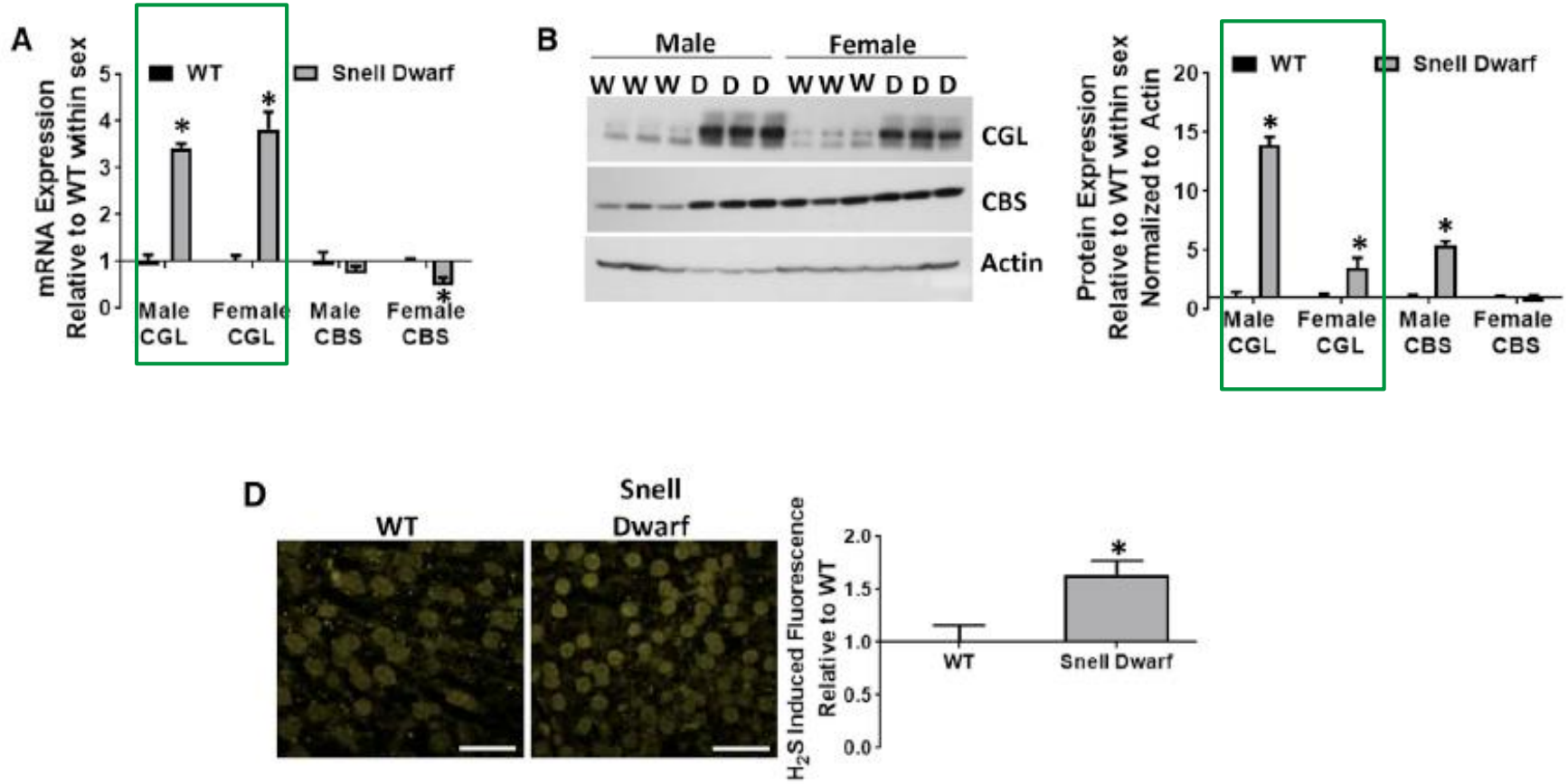
Hine C, *et al*., Cell Metabolism 2017; 25:1320-1333

Thyroid hormone & hepatic H_2S production



Hine C, *et al*., Cell Metabolism 2017; 25:1320-1333

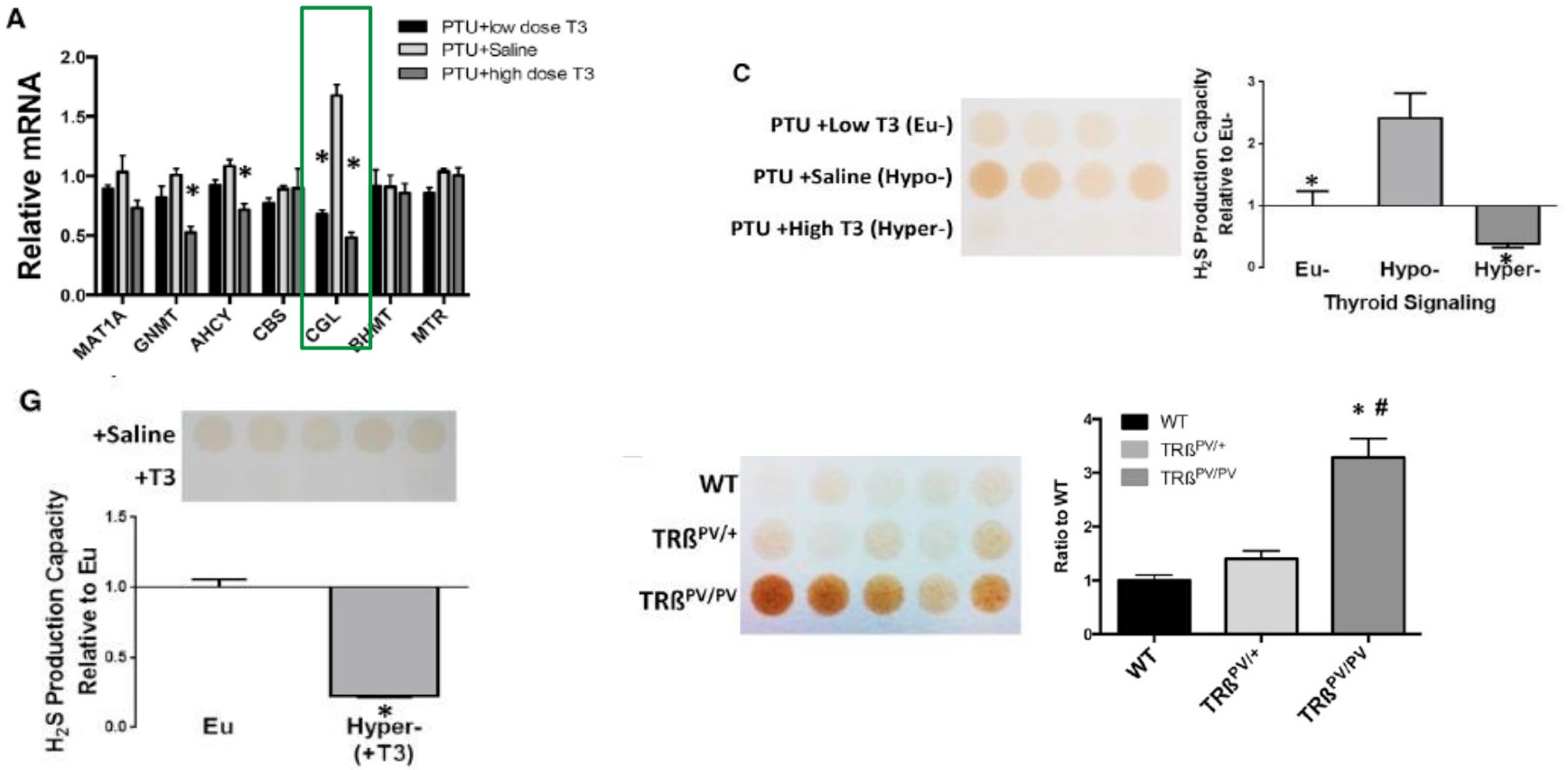
Thyroid hormone & hepatic H_2S production



➡ TSH and GH deficiency/inhibition promote hepatic H_2S production *in vivo*

Hine C, *et al*., Cell Metabolism 2017; 25:1320-1333

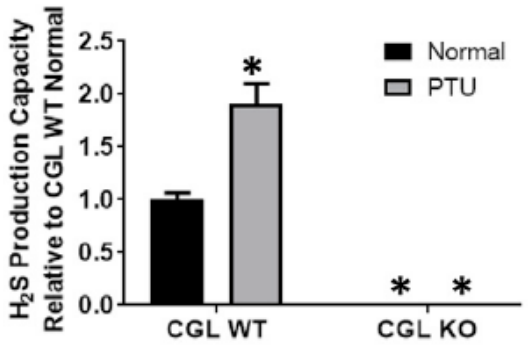
Thyroid hormone & hepatic H_2S production

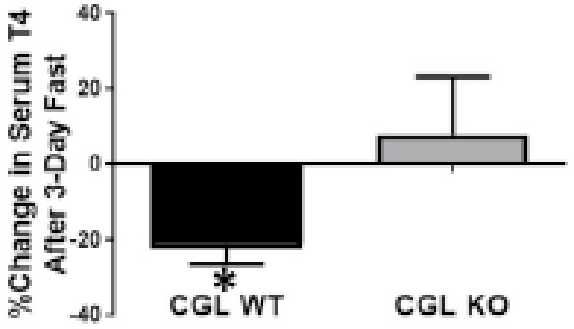


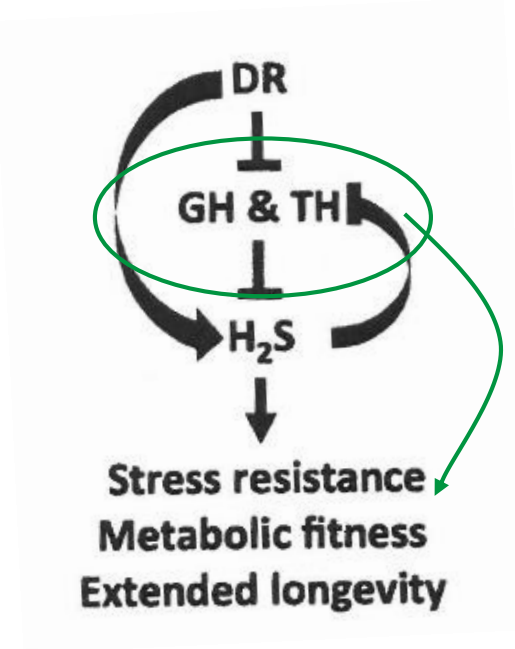
➡ Hypothyroidism increases / thyroid hormone represses hepatic H_2S production *in vivo* via TRβ1

Hine C, *et al*., Cell Metabolism 2017; 25:1320-1333

Thyroid hormone & hepatic H_2S production







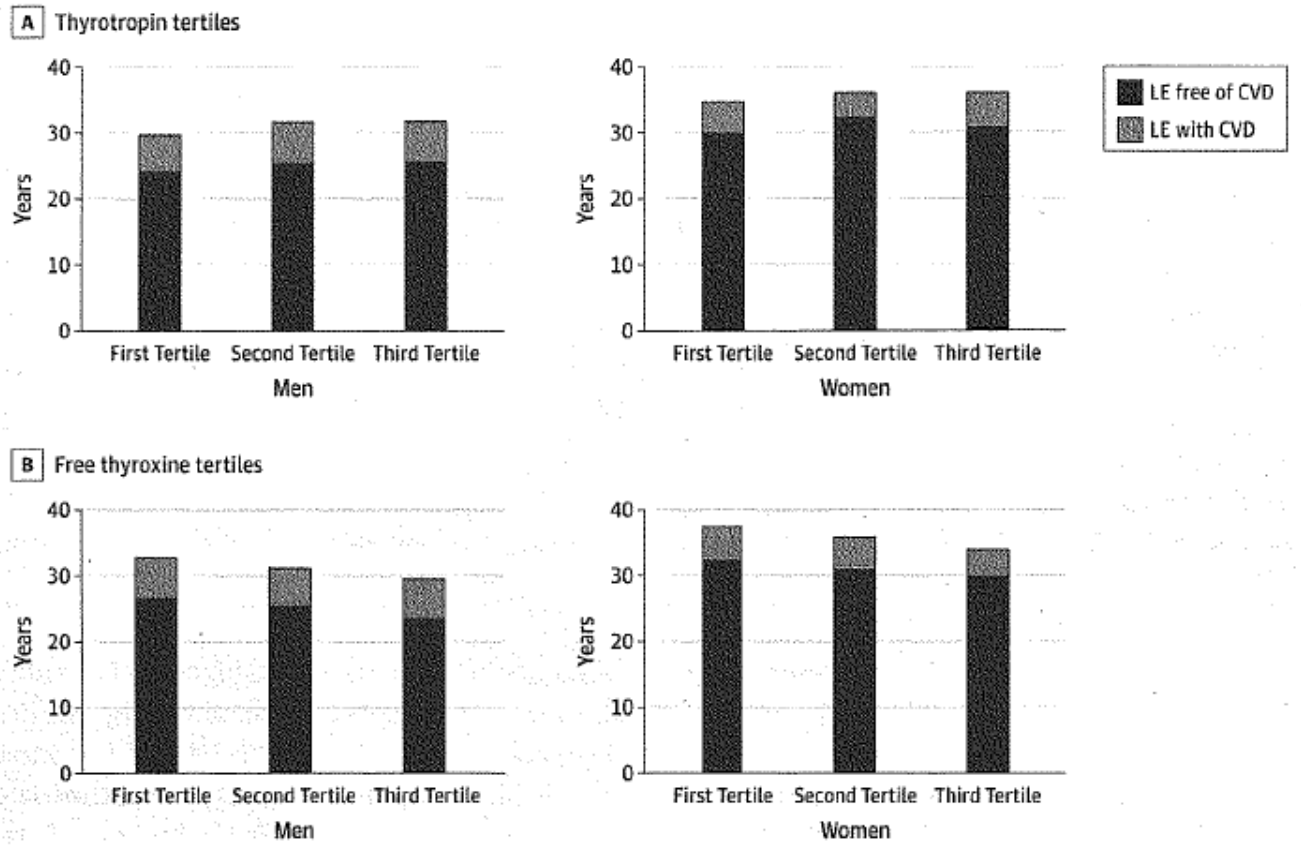
- TH / GH are negative regulators of H_2S production
- TH / GH signaling could be the link between DR and H_2S production
- H_2S is involved in negative regulation of TH / GH signaling, key longevity associated hormones = potential mechanism of H_2S action and mediator of its beneficial effects

Hine C, *et al*., Cell Metabolism 2017; 25:1320-1333

Thyroid hormone & key longevity associated hormone

Rotterdam Study

Figure. Life Expectancy (LE) With and Without Cardiovascular Disease (CVD) at Age 50 Years Among Thyrotropin and Free Thyroxine Tertiles, in Men and Women

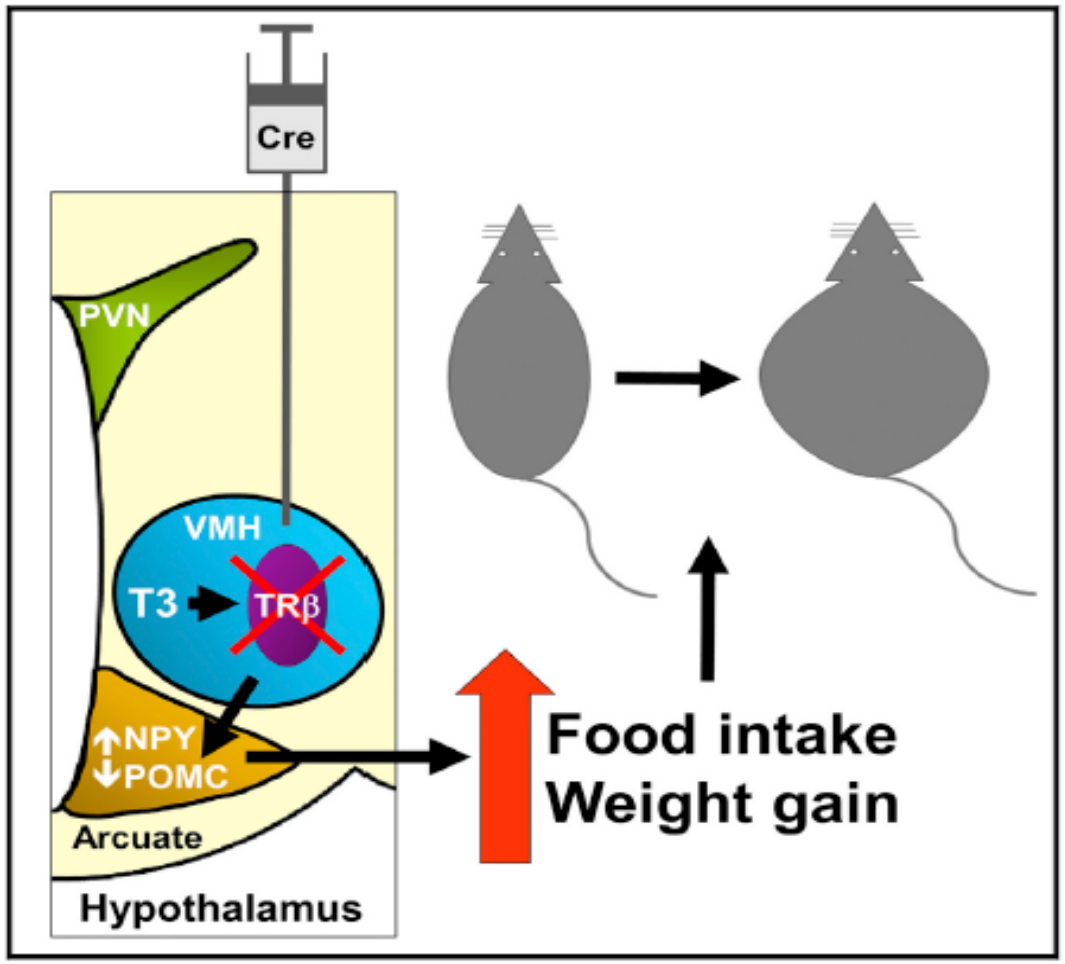


Bano A, *et al*., JAMA Intern Med 2017; 11:1650-1657

Cell Reports

Thyroid Hormone Receptor Beta in the Ventromedial Hypothalamus Is Essential for the Physiological Regulation of Food Intake and Body Weight

Graphical Abstract



Authors

Saira Hameed, Michael Patterson, Waljit S. Dhillo, ..., J.H. Duncan Bassett, Graham R. Williams, James V. Gardiner

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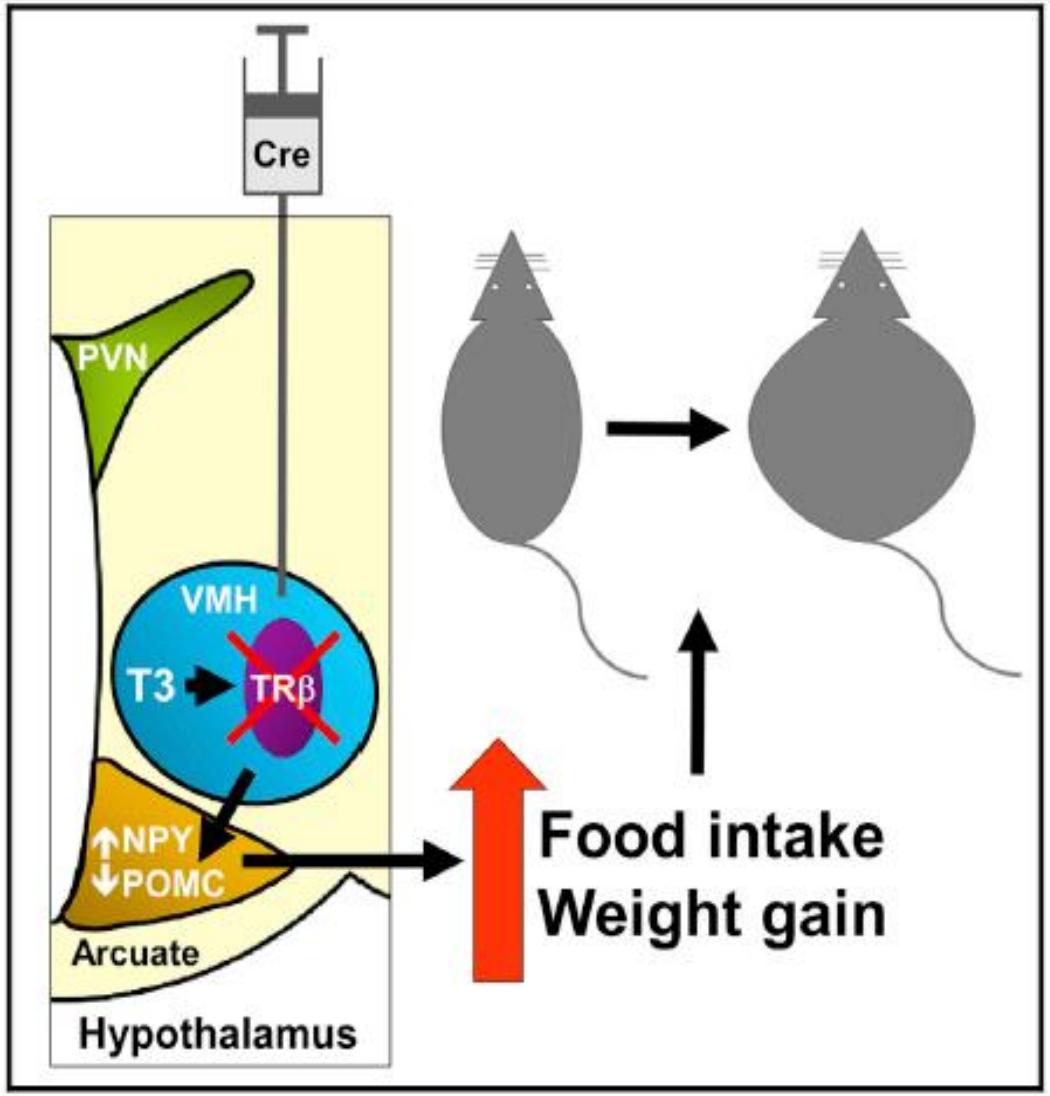
graham.williams@imperial.ac.uk (G.R.W.), j.gardiner@imperial.ac.uk (J.V.G.)

In Brief

Hameed et al. report that selective knockdown of a thyroid hormone receptor in the mouse hypothalamus results in a phenotype of severe obesity, overeating, and reduced energy expenditure, which may be due to downstream changes in the expression of hypothalamic regulators of food intake.

Hameed S, *et al.*, Cell Reports 2017; 19:2202-2209

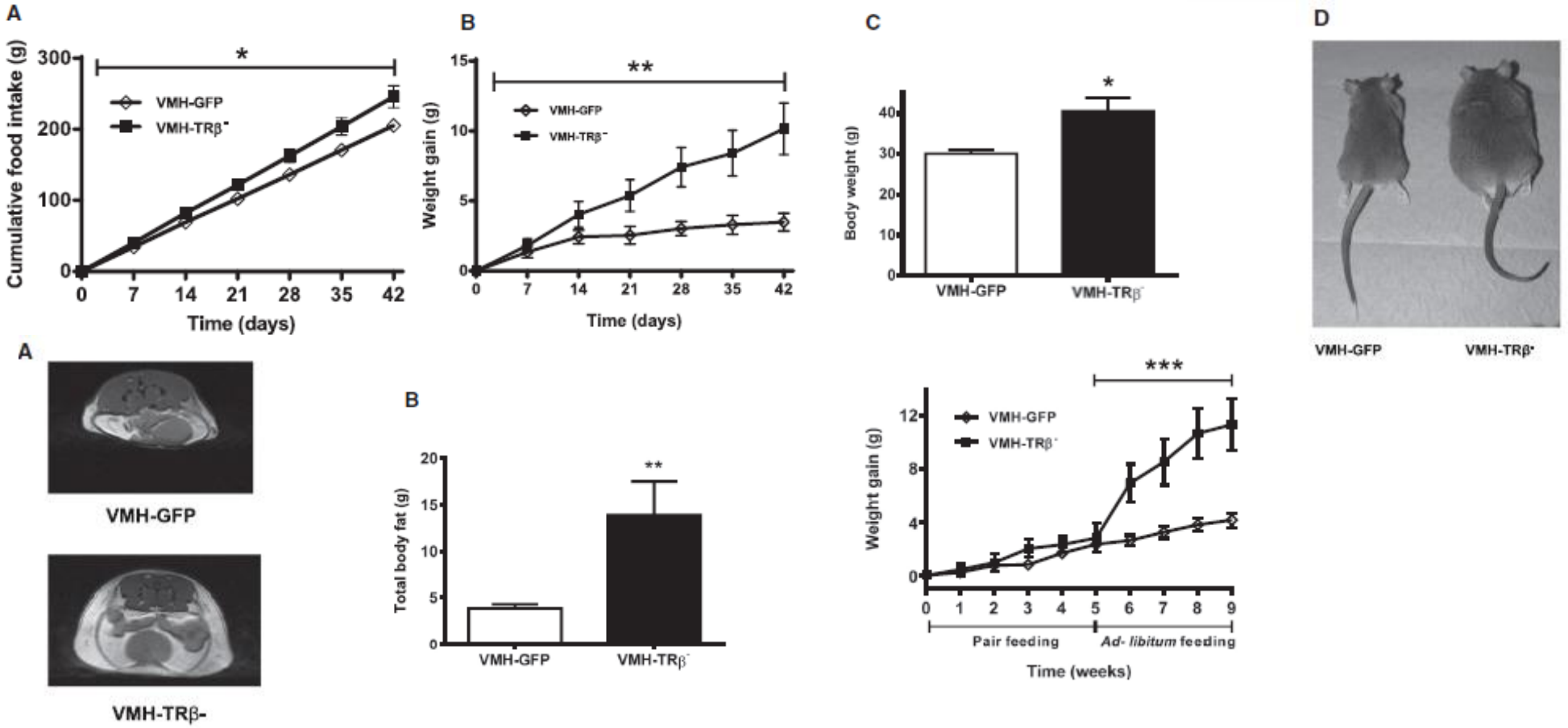
TRβ in VMH & Regulation of food intake



- Improved understanding of the mechanisms that regulate appetite and body weight ⟶ design of anti-obesity therapies
- The TR-beta isoform (TRβ) is expressed in the ventromedial hypothalamus (VMH)- a brain area important for control of energy homeostasis

Hameed S, *et al*., Cell Reports 2017; 19:2202-2209

TRβ in VMH & Regulation of food intake



- TRβ knockdown in the VMH results in a phenotype of hyperphagia comparable to some of the most extreme forms of monogenic obesity
- Hypothalamic TRβ major physiological regulator of energy homeostasis

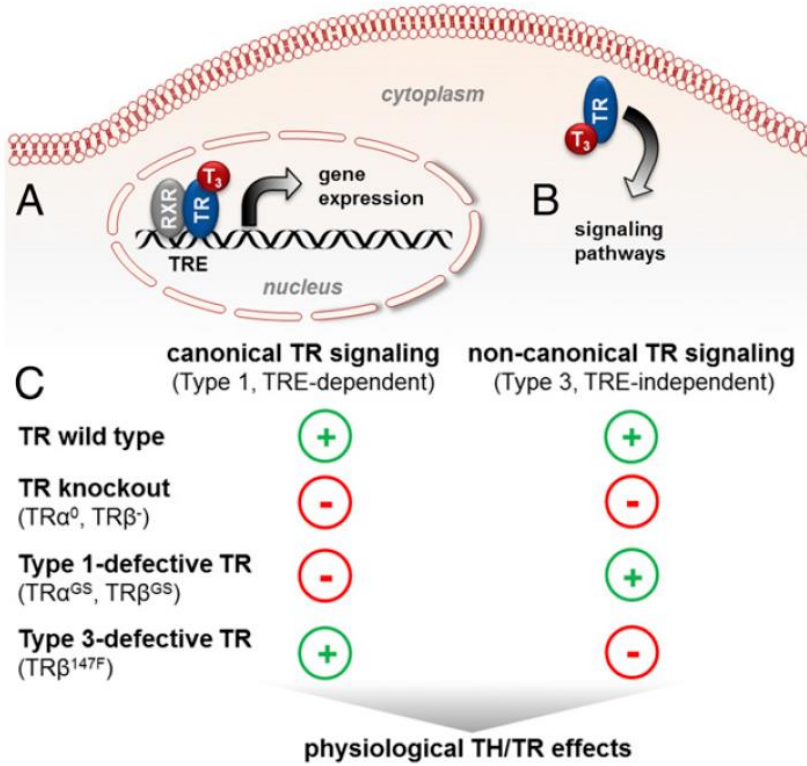
Hameed S, *et al.*, Cell Reports 2017; 19:2202-2209

Non-classical thyroid hormone action
Novel thyroid hormone targets

Noncanonical thyroid hormone signaling mediates cardiometabolic effects in vivo

G. Sebastian Hönes[a], Helena Rakov[a], John Logan[b], Xiao-Hui Liao[c], Eugenie Werbenko[b], Andrea S. Pollard[b], Stine M. Præstholm[d], Majken S. Siersbæk[d], Eddy Rijntjes[e], Janina Gassen[a], Sören Latteyer[a], Kathrin Engels[a], Karl-Heinz Strucksberg[a], Petra Kleinbongard[f], Denise Zwanziger[a], Jan Rozman[g,h], Valerie Gailus-Durner[g], Helmut Fuchs[g], Martin Hrabe de Angelis[g,h,i], Ludger Klein-Hitpass[j], Josef Köhrle[e], David L. Armstrong[k], Lars Grøntved[d], L. H. Duncan Bassett[b], Graham R. Williams[b], Samuel Refetoff[c,l,m], Dagmar Führer[a], and Lars C. Moeller[a,1]

[a]al Essen, University of Duisburg-Essen, 45147 Essen, Germany; [b]Molecular on, London W12 0NN, United Kingdom; [c]Department of Medicine, The Molecular Biology, University of Southern Denmark, 5230 Odense, Denmark; Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Institut für ysiology, West-German Heart and Vascular Center Essen, University Hospital Essen, , Institute of Experimental Genetics, Helmholtz Zentrum München, German German Center for Diabetes Research, 85764 Neuherberg, Germany; [i]Chair of niversität München, 85354 Freising, Germany; [j]Institute of Cell Biology (Cancer ermany; [k]Laboratory of Neurobiology, National Institute of Environmental Health 9; [l]Department of Pediatrics, The University of Chicago, Chicago, IL 60637;



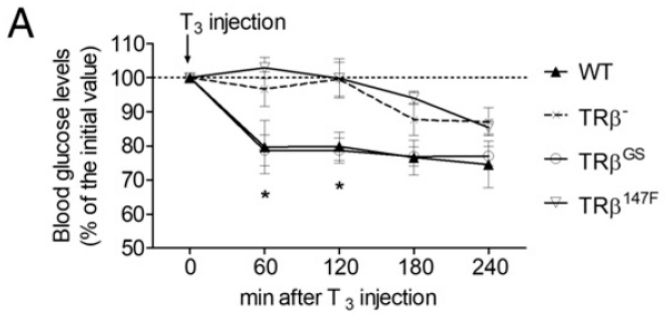
Establishment of

- $TR\alpha^{GS}$ and $TR\beta^{GS}$ mice with loss of canonical TR signaling
- $TR\beta^{147F}$ with abolished non-canonical TRβ signaling

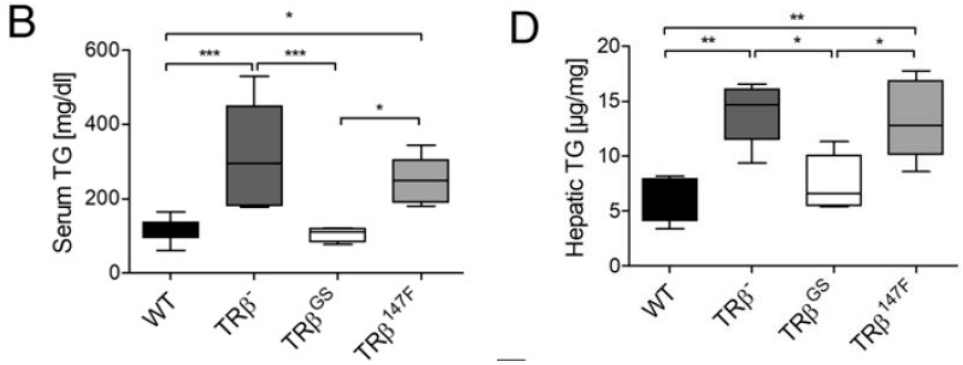
Hönes GS, *et al.*, PNAS 2017; 114:E11323-E11332

Noncanonical TRβ signaling

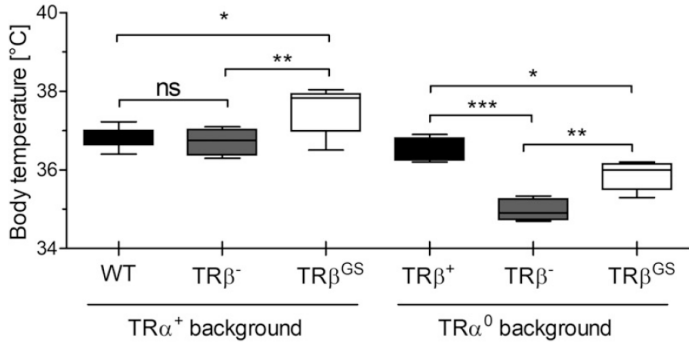
Blood glucose



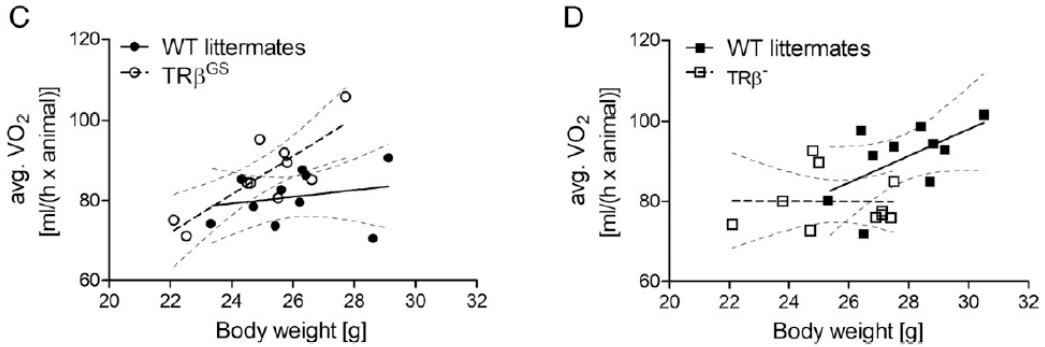
Serum and liver triglyceride concentration



Body temperature



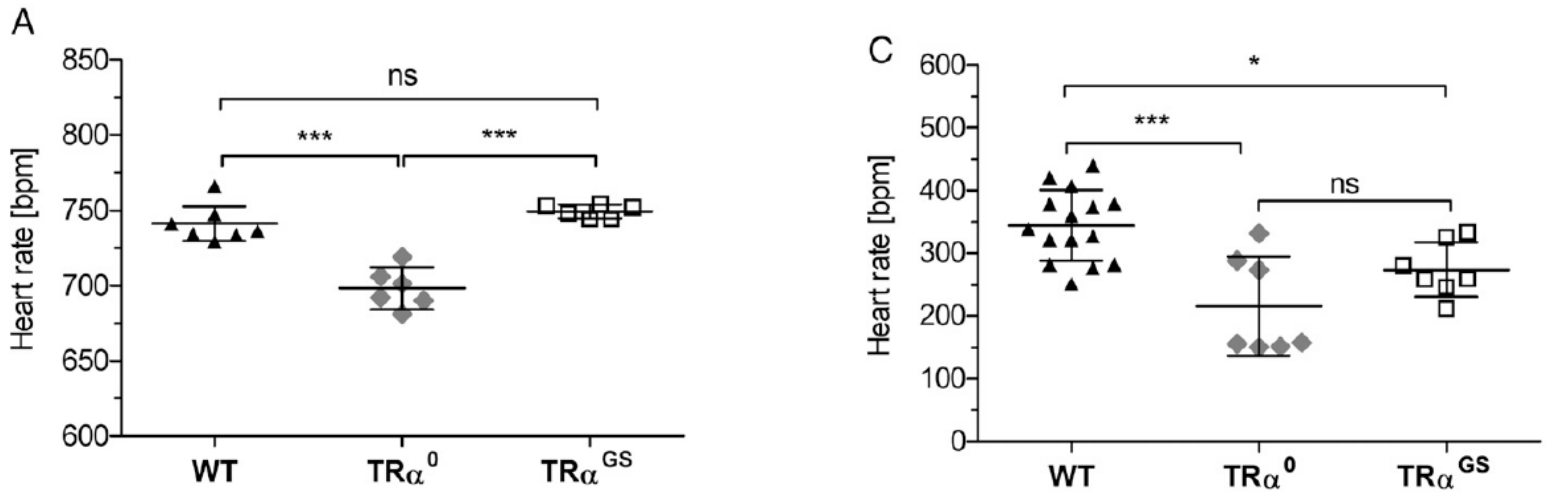
Oxygen consumption



Hönes GS, *et al.*, PNAS 2017; 114:E11323-E11332

Noncanonical TRα signaling

Basal heart rate



- Noncanonical TR signaling contributes significantly to physiologic actions of TH
- Noncanonical TR signaling predominantly regulates energy homeostasis
- Profound implications for the role of TRs in metabolism and physiology
- Explain the pathophysiology in diseases caused by the various TR mutations
- Paradigm shift for TH action

Hönes GS, *et al.*, PNAS 2017; 114:E11323-E11332

nature medicine

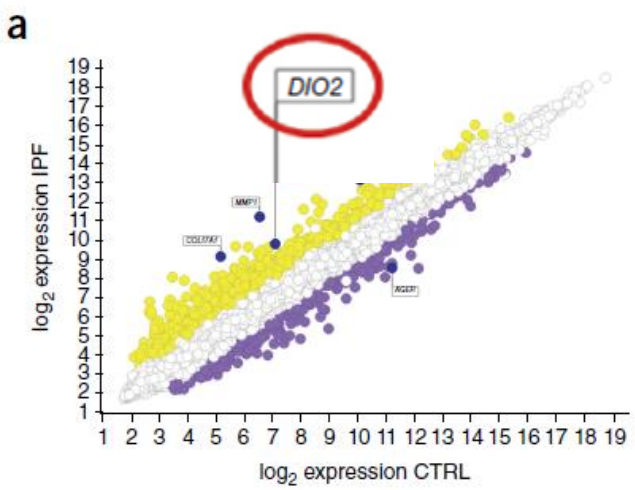
Thyroid hormone inhibits lung fibrosis in mice by improving epithelial mitochondrial function

Guoying Yu[1,11], Argyris Tzouvelekis[1,2,11], Rong Wang[1,10], Jose D Herazo-Maya[1], Gabriel H Ibarra[1], Anup Srivastava[1], Joao Pedro Werneck de Castro[3,4], Giuseppe DeIuliis[1], Farida Ahangari[1], Tony Woolard[1], Nachelle Aurelien[1], Rafael Arrojo e Drigo[5], Ye Gan[1], Morven Graham[6], Xinran Liu[6], Robert J Homer[7,8], Thomas S Scanlan[9], Praveen Mannam[1], Patty J Lee[1], Erica L Herzog[1], Antonio C Bianco[3] & Naftali Kaminski[1]

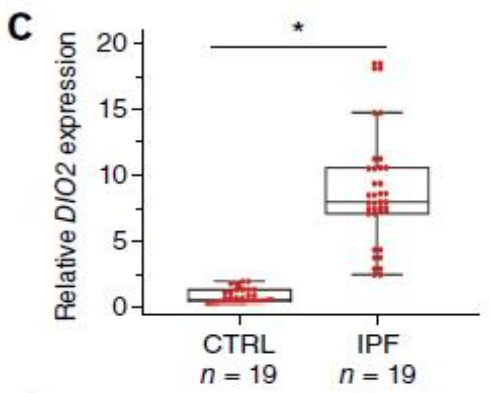
Yu, G *et al.*, Nature Med 2018; 24:39-49

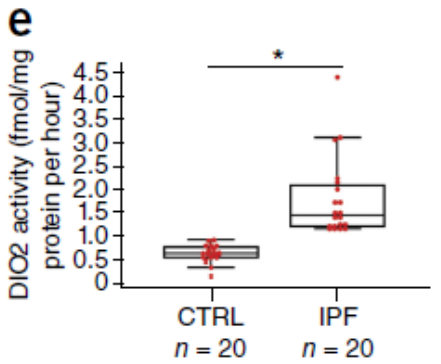
Thyroid hormone & lung fibrosis

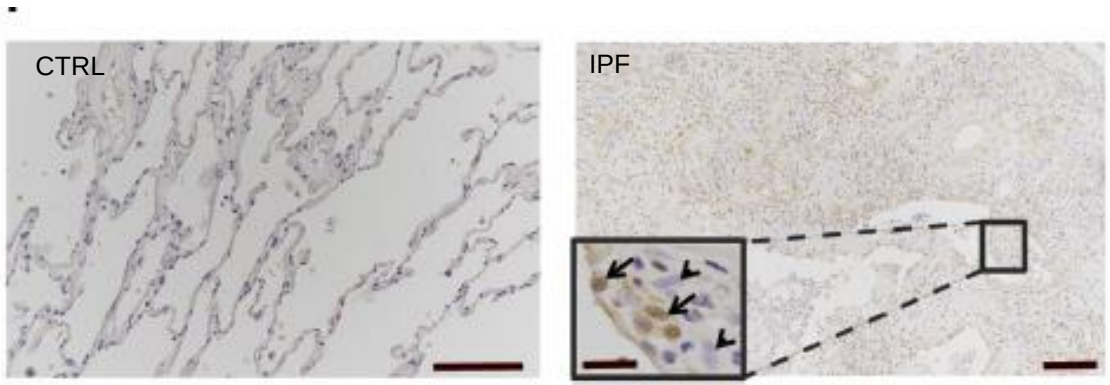
DIO2 expression and activity in IPF patient lungs

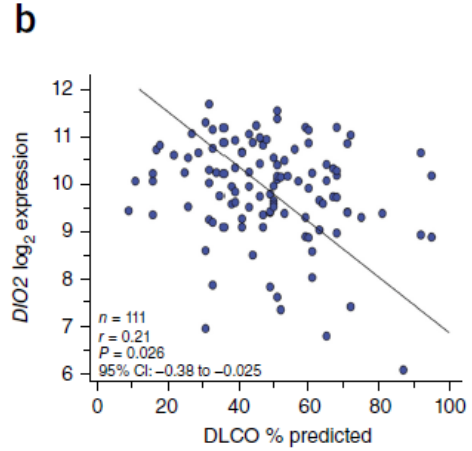


Lung Genomic Research Consortium data set





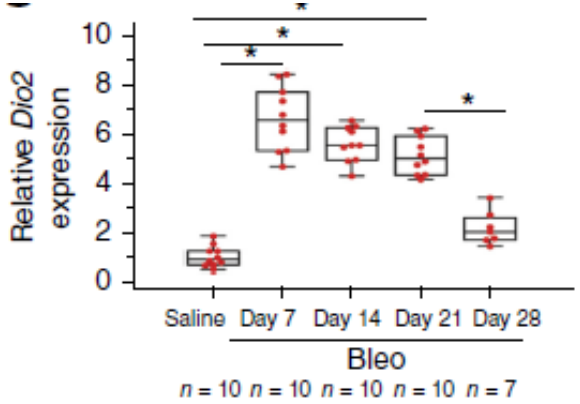


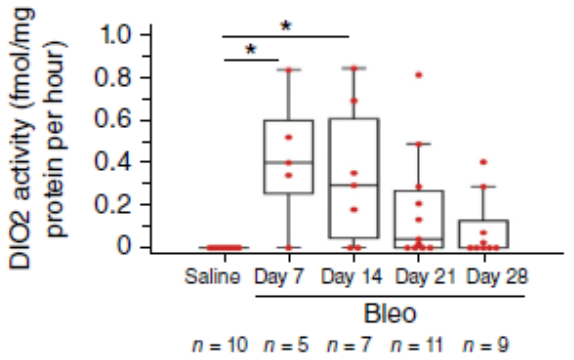


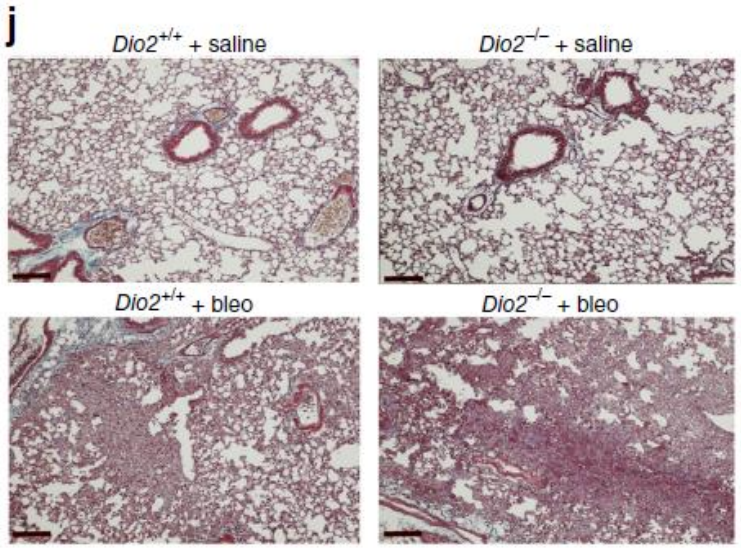
Yu, G *et al.*, Nature Med 2018; 24:39-49

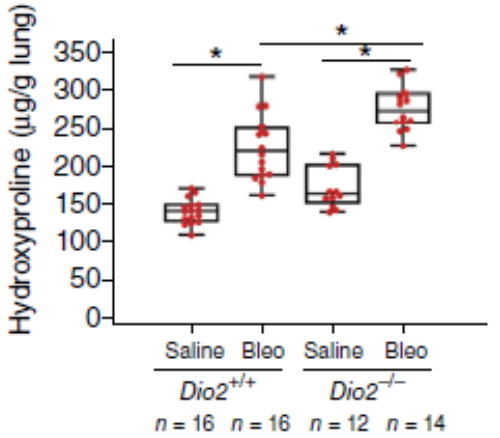
Thyroid hormone & lung fibrosis

DIO2 expression and activity in IPF mouse model (bleomycin model of lung fibrosis)





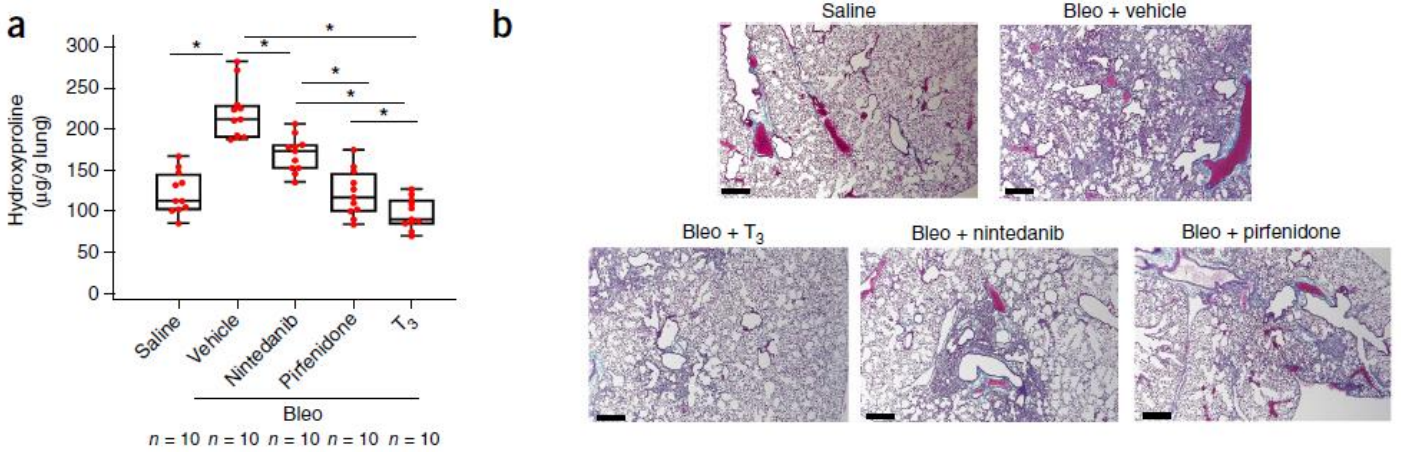


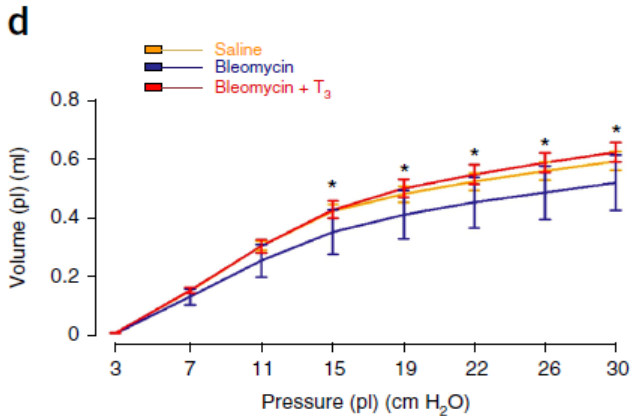


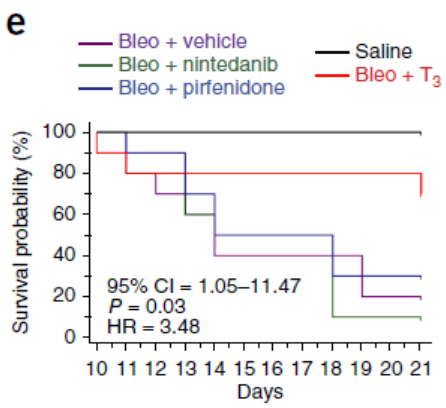
Yu, G *et al.*, Nature Med 2018; 24:39-49

Thyroid hormone & lung fibrosis

Aerosolized T3 treatment in IPF mouse models







- T3 blunts lung fibrosis
- T3 reverses bleomycin-induced mitochondrial changes
- T3 suppresses mitochondria-regulated apoptosis
- Upregul. of DIO2 = effort to boost local conversion of T4 to T3

➡ New role of thyroid hormone as potential therapeutic agent in IPF

Yu, G *et al.*, Nature Med 2018; 24:39-49

Thyroid cancer

Precision Medicine and Imaging

Clinical Cancer Research

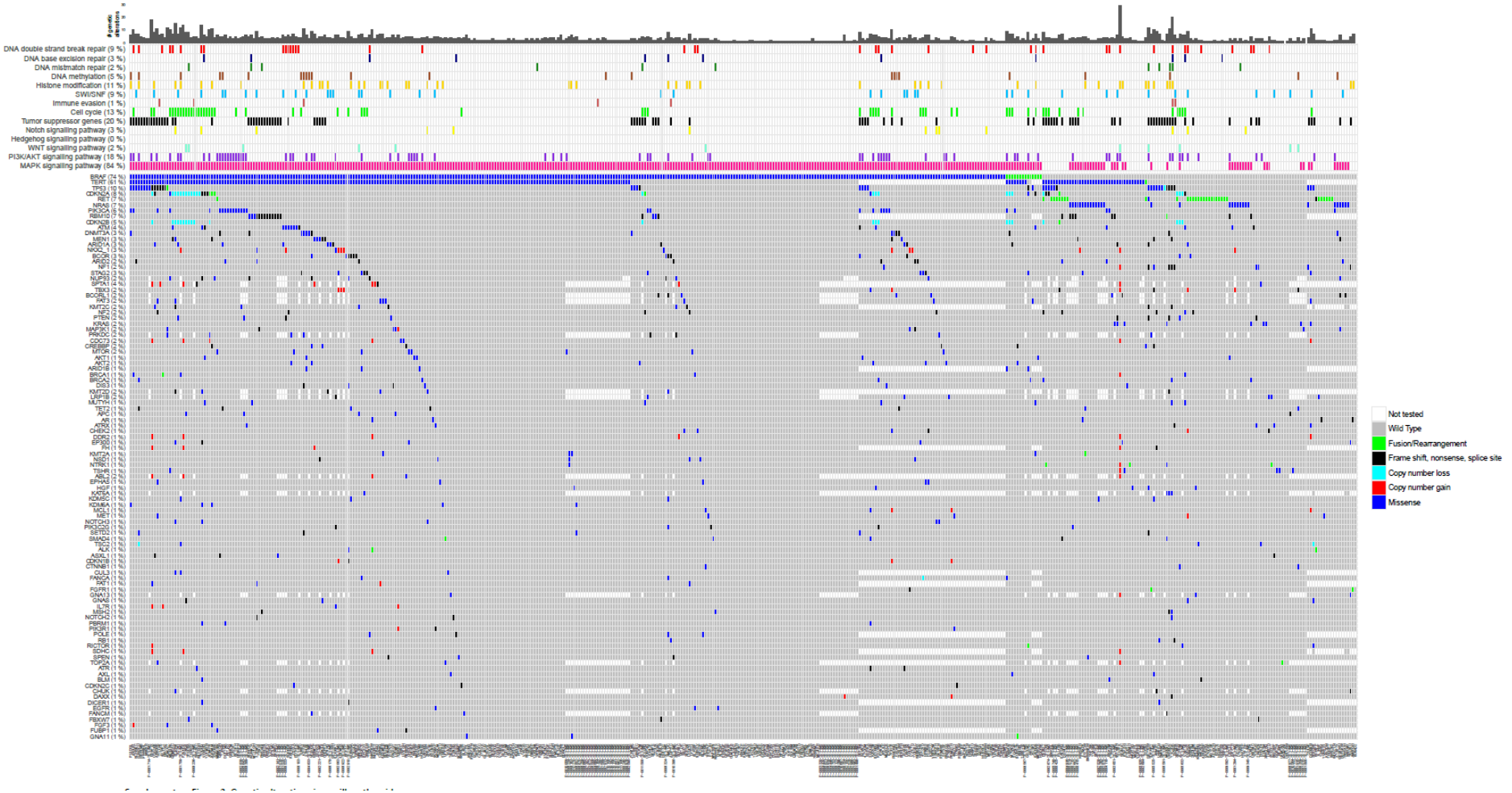
Genetic Analysis of 779 Advanced Differentiated and Anaplastic Thyroid Cancers

Nikita Pozdeyev[1,2,3], Laurie M. Gay[4], Ethan S. Sokol[4], Ryan Hartmaier[4], Kelsi E. Deaver[1], Stephanie Davis[1,5], Jena D. French[1,3], Pierre Vanden Borre[4], Daniel V. LaBarbera[3,6], Aik-Choon Tan[3,7], Rebecca E. Schweppe[1,3], Lauren Fishbein[1,2,3], Jeffrey S. Ross[4,8], Bryan R. Haugen[1,3], and Daniel W. Bowles[3,7]

Check for updates

Genetic profiling of advanced DTC and ATC

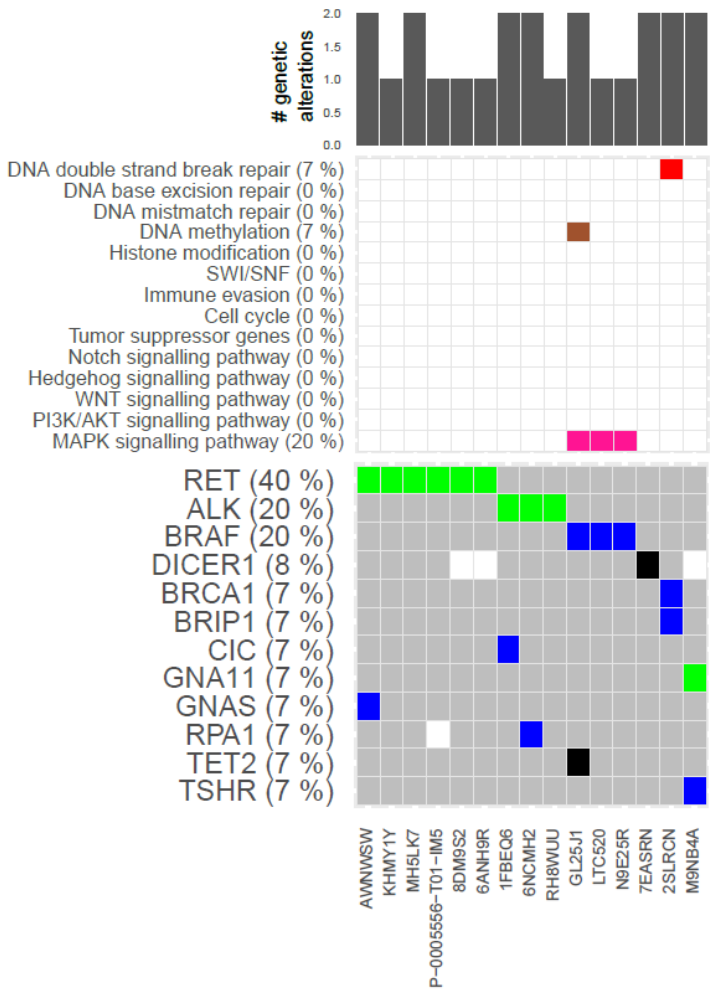
PTC

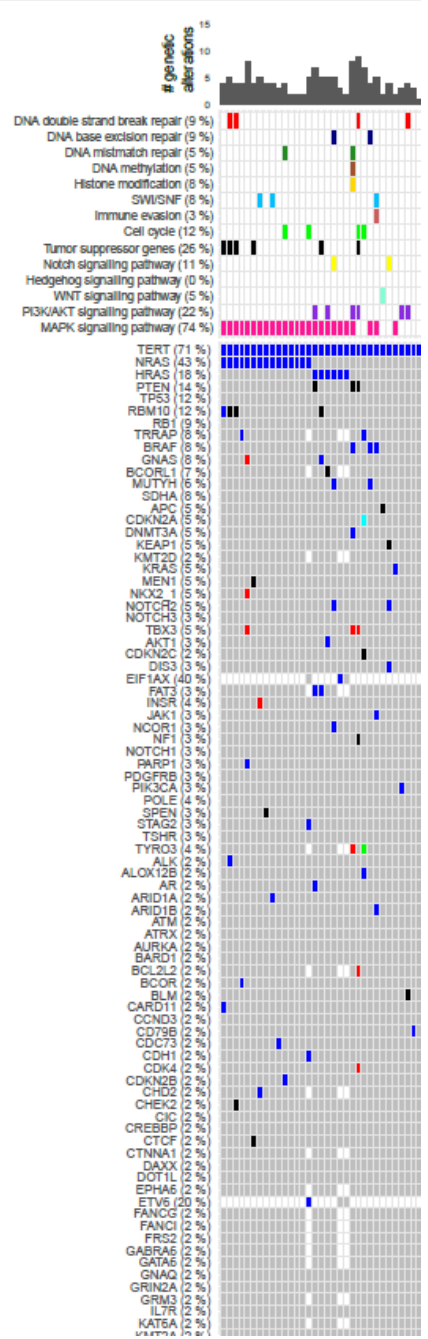


Pozdeyev N, *et al.*, Clin Cancer Res 2018; 24:3059-3068

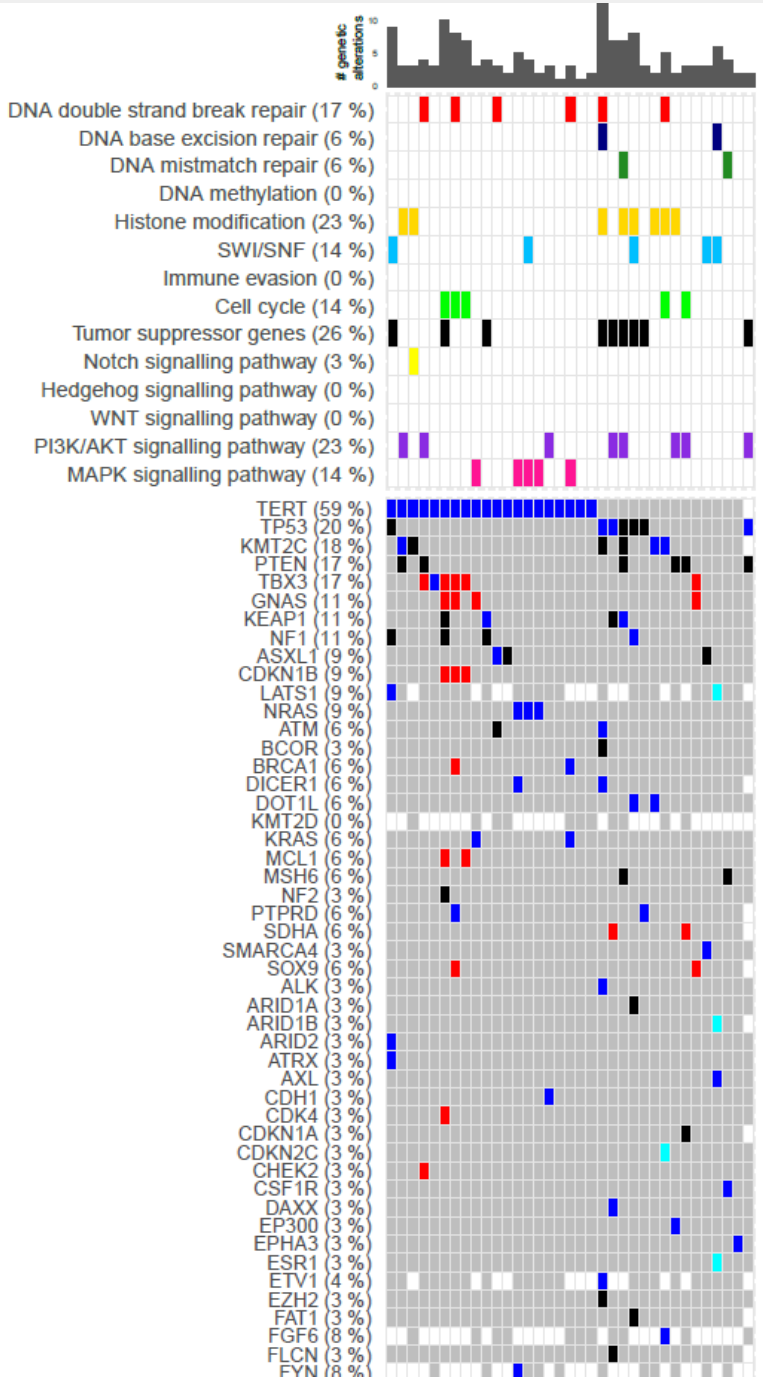
LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN

Pediatric PTC





HCTC



Pozdeyev N, *et al.*, Clin Cancer Res 2018; 24:3059-3068

Genetic profiling of advanced DTC and ATC

ATC

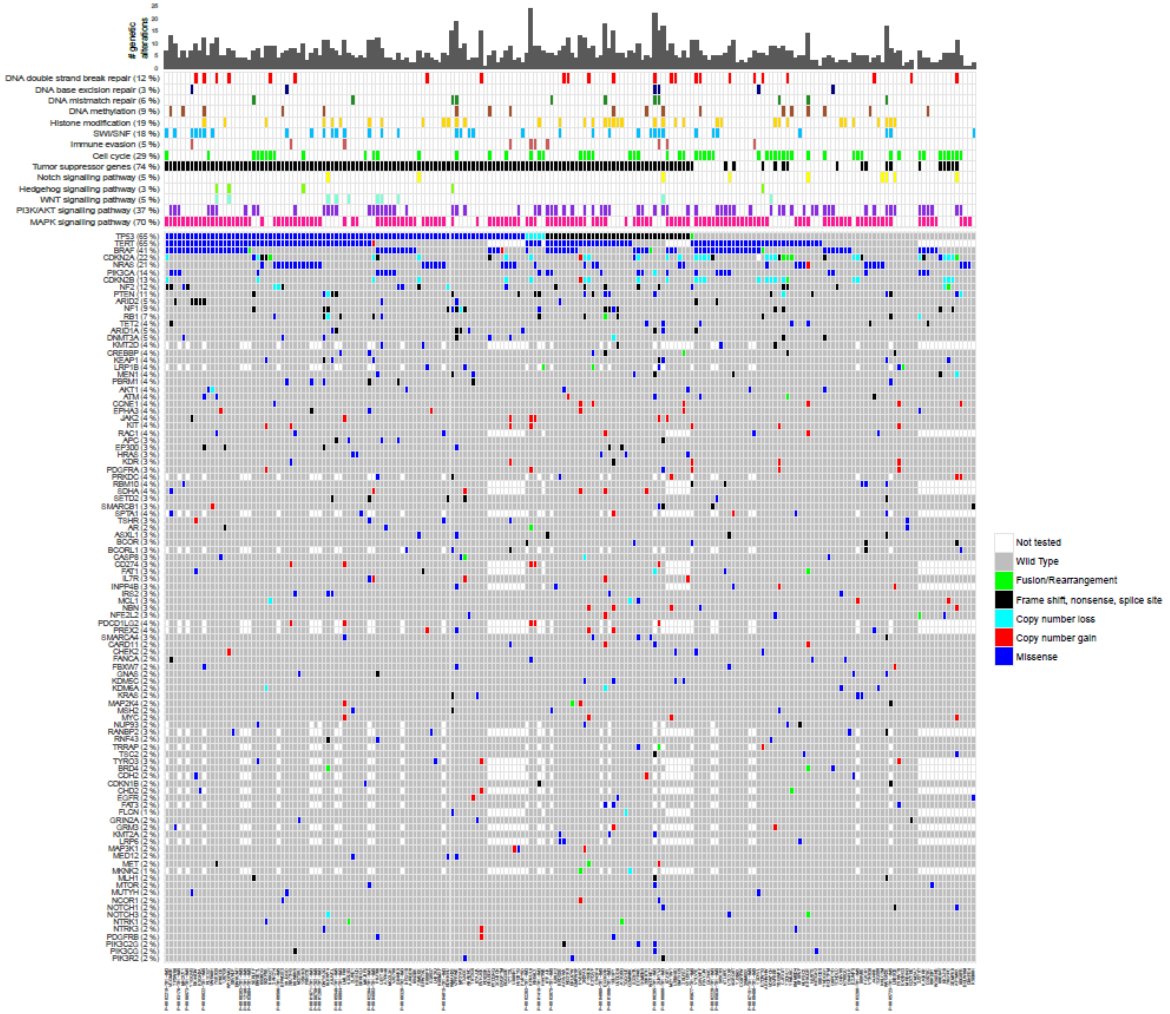


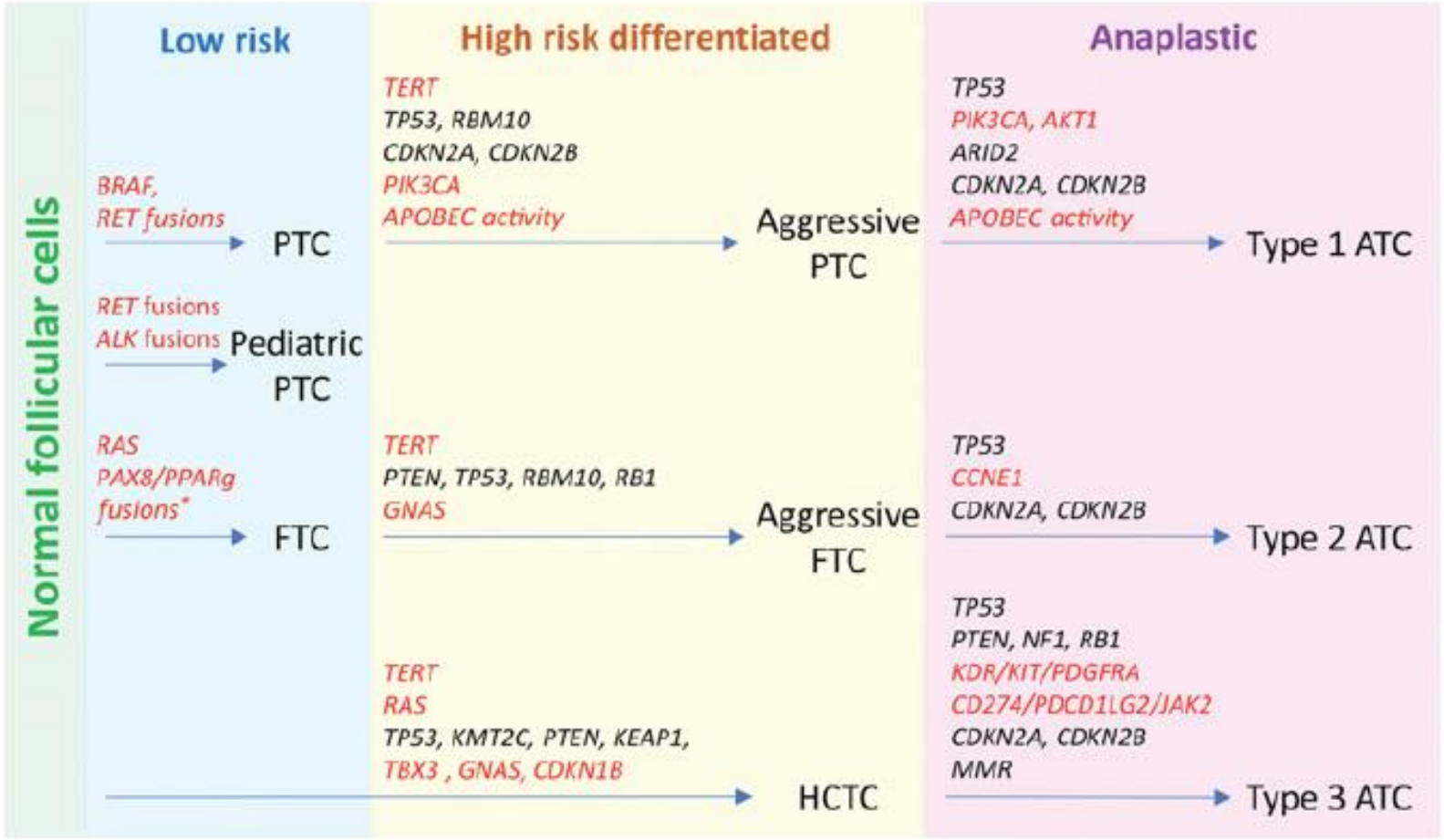
Table 3. Pathways and genes more frequently altered in ATC than in DTC

Gene or group of genes	Prevalence, % DTC	ATC	*P*[a]
Tumor suppressors	21	74	1.45e−38
TP53	11	65	2.77e−50
NF2	2	12	4.26e−06
RB1	2	7	0.01
NF1	3	9	0.01
Cell-cycle pathway	13	29	7.42e−10
CDKN2A	7	22	4.29e−06
CDKN2B	4	13	0.001
CCNE1	0	4	0.001
PI3K/AKT pathway	18	37	9.50e−06
PIK3CA	5	14	0.002
PTEN	4	11	0.01
SWI/SNF nucleosome modification pathway	9	18	0.007
PBRM1	1	4	0.01
Immune evasion	2	5	0.07
CD274	0	3	0.03
PDCD1LG2	0	4	0.01
JAK2	1	4	0.03
Hedgehog signaling pathway	0	3	0.009
Histone modification	11	19	0.03
Mutation-high genotype	2	6	0.05
RAC1	0	4	0.004
KIT	0	4	0.004
KDR	0	3	0.03
PDGFRA	0	3	0.03
INPP4B	0	3	0.009
NFE2L2	0	3	0.03
CASP8	0	3	0.03
EPHA3	1	4	0.03
NBN	0	3	0.03

NOTE: Signaling pathways and groups of genes are highlighted in bold.
[a]χ^2, *P* values were adjusted for multiple comparisons using Benjamini–Hochberg method.

Pozdeyev N, *et al.*, Clin Cancer Res 2018; 24:3059-3068

Genetic profiling of advanced DTC and ATC

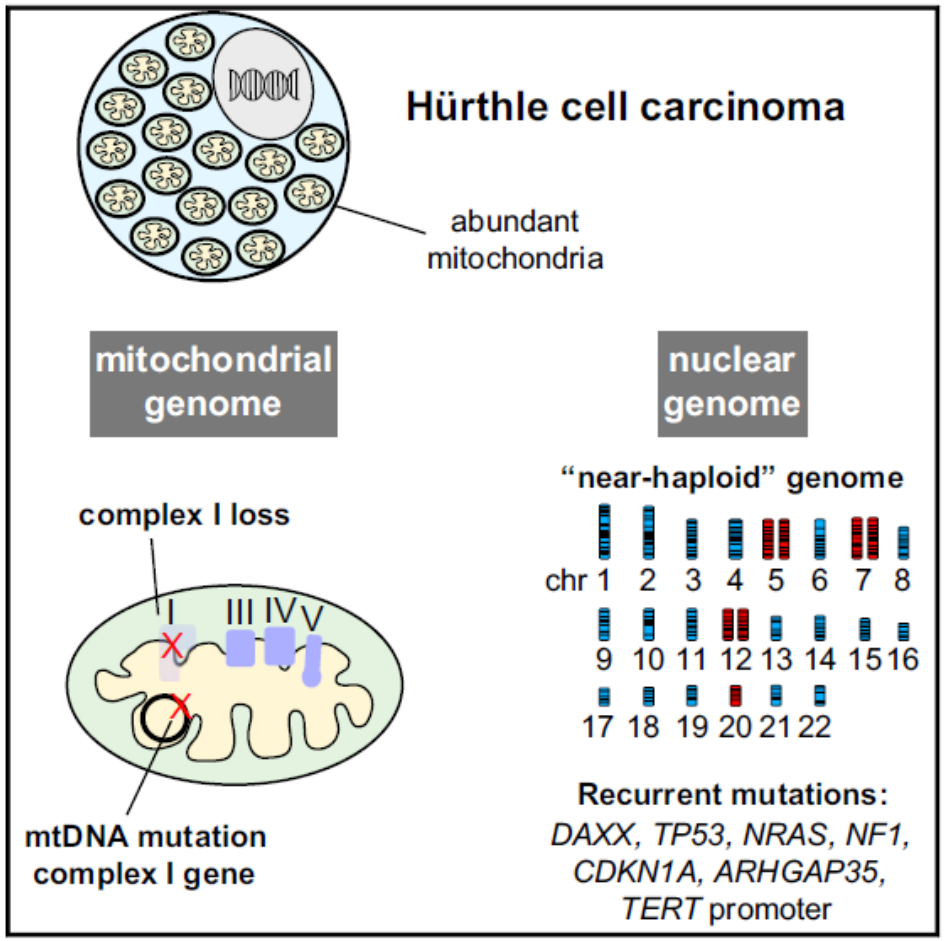


Pozdeyev N, *et al.*, Clin Cancer Res 2018; 24:3059-3068

Cancer Cell

Widespread Chromosomal Losses and Mitochondrial DNA Alterations as Genetic Drivers in Hürthle Cell Carcinoma

Graphical Abstract



Authors

Raj K. Gopal, Kirsten Kübler, Sarah E. Calvo, ..., Dora Dias-Santagata, Gad Getz, David G. McFadden

Correspondence

gadgetz@broadinstitute.org (G.G.), david.mcfadden@utsouthwestern.edu (D.G.M.)

In Brief

Gopal et al. identify recurrent alterations in *DAXX*, *TP53*, *NRAS*, *NF1*, *CDKN1A*, *ARHGAP35*, and the *TERT* promoter, as well as in mtDNA-encoding complex I of the electron transport chain, in Hürthle cell carcinomas (HCC). Many HCCs harbor widespread chromosomal loss culminating in a near-haploid state.

Gopal RK, *et al.*, Cancer Cell 2018; 34:242-255

le Cell Cancer Mitochondrial Landscapes

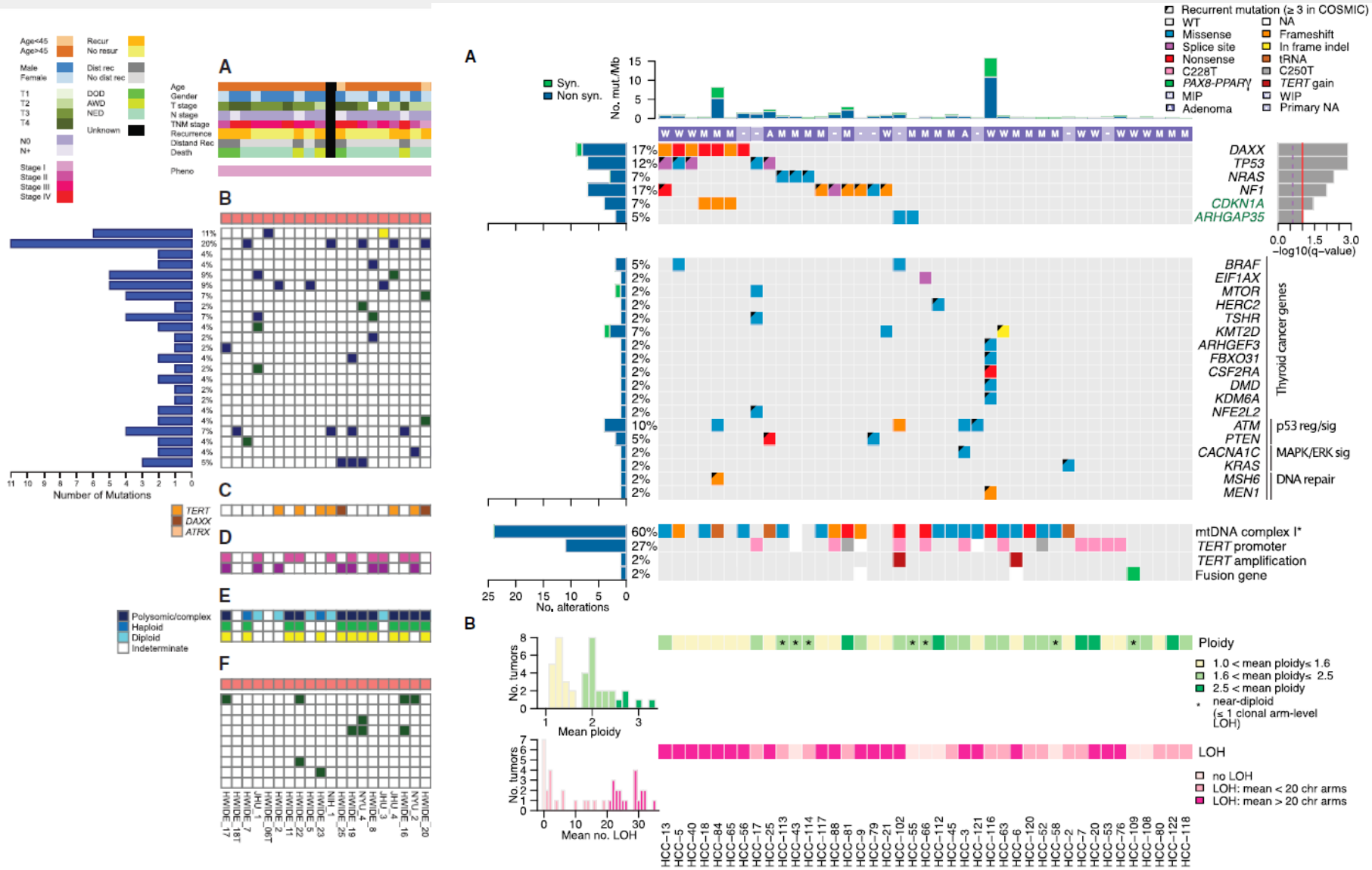
ladimir Makarov, ad Deraje, ..., ssein, James A. Fagin, Chan

ndence

cc.org (I.G.), cc.org (T.A.C.)

Ganly I, *et al.*, Cancer Cell 2018; 34:256-270

Genetic profiling of Hurthle cell cancer



Ganly I, *et al.*, Cancer Cell 2018; 34:256-270
Gopal RK, *et al.*, Cancer Cell 2018; 34:242-255

The Journal of Clinical Investigation

RESEARCH ARTICLE

Hgf/Met activation mediates resistance to BRAF inhibition in murine anaplastic thyroid cancers

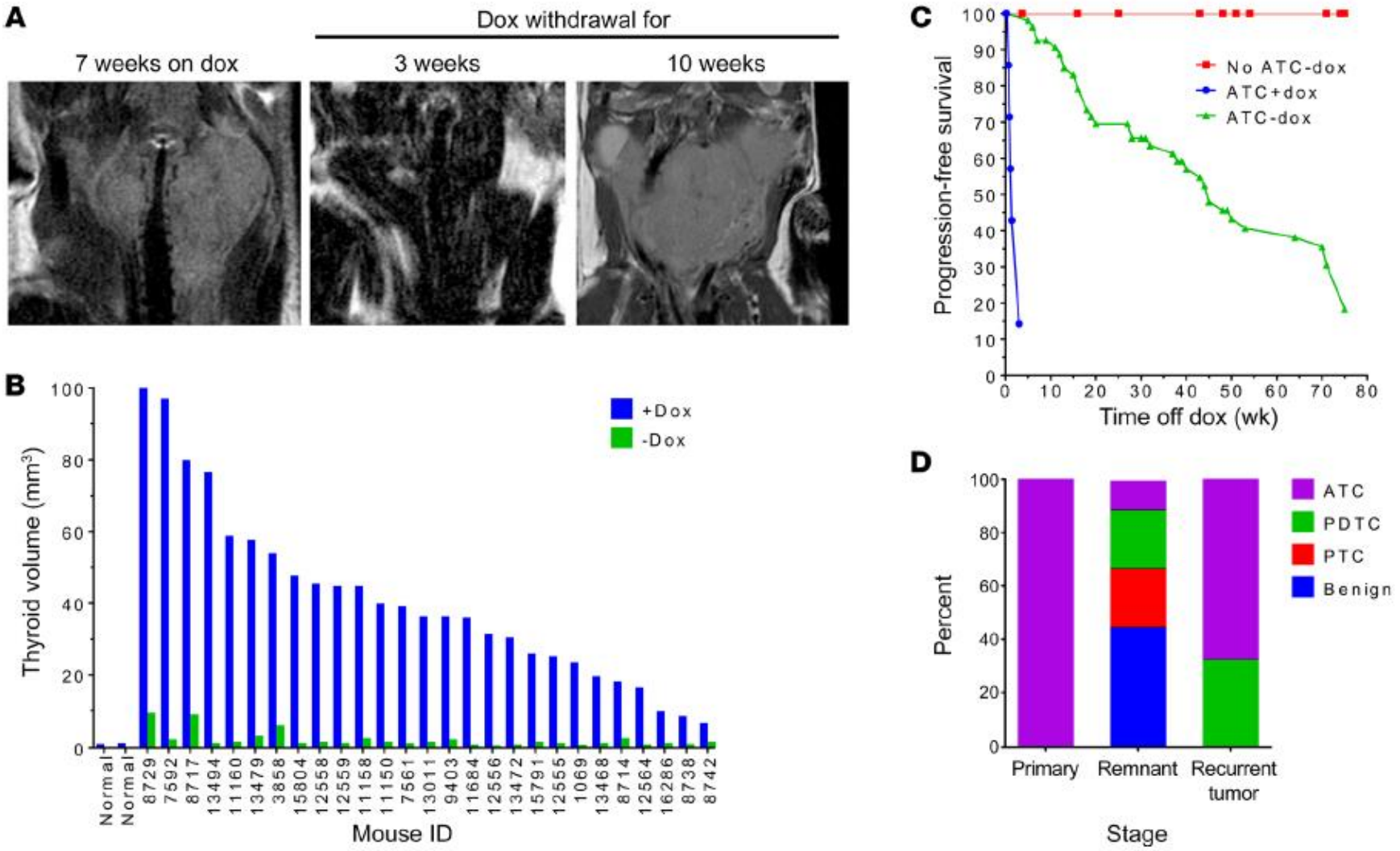
Jeffrey A. Knauf,[1,2] Kathleen A. Luckett,[1] Kuen-Yuan Chen,[1] Francesca Voza,[1] Nicholas D. Socci,[3] Ronald Ghossein,[4] and James A. Fagin[1,2,5]

[1]Human Oncology and Pathogenesis Program, [2]Department of Medicine, [3]Bioinformatics Core, and [4]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, New York, USA.

[5]Department of Medicine, Weill-Cornell Medical College, New York, New York, USA.

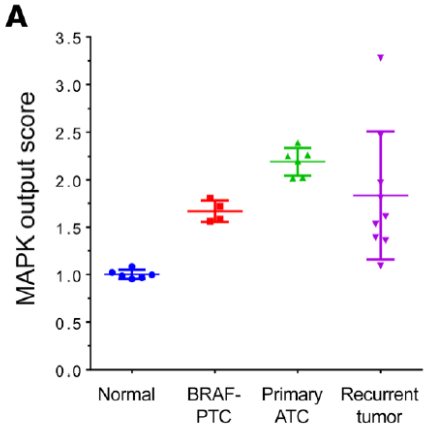
Knauf JA, *et al.*, J Clin Invest 2018; 128:4086-4097

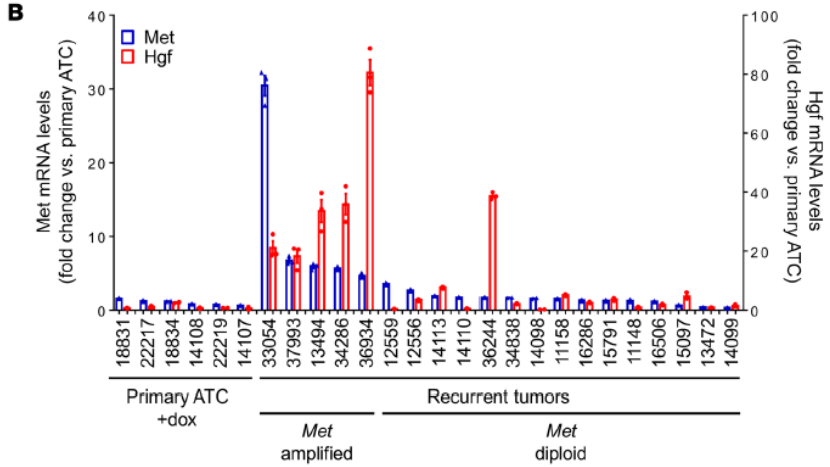
Resistance to BRAF inhibition in ATC

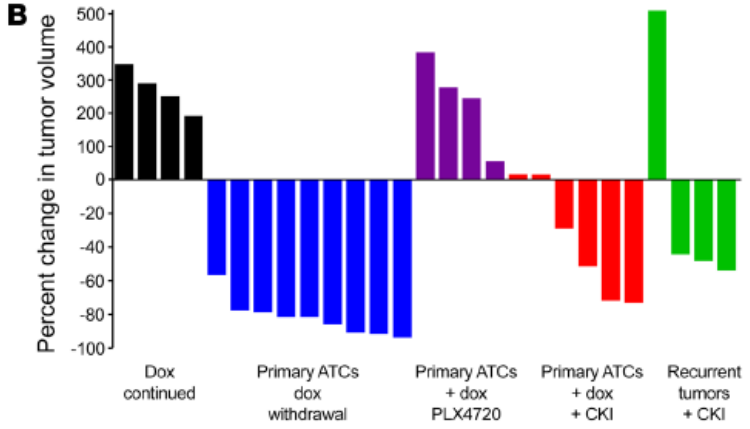


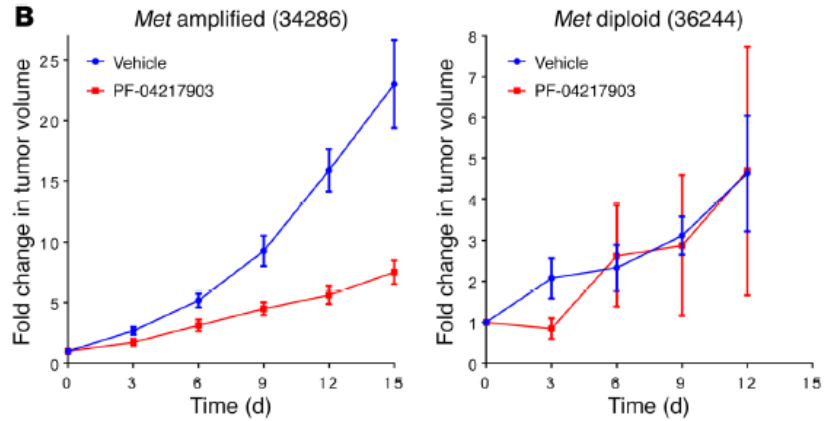
Knauf JA, *et al.*, J Clin Invest 2018; 128:4086-4097

Resistance to BRAF inhibition in ATC









➡ Resistance to BRAF inhibition involves activation of HGF/Met signaling that can be targeted by MET inhibitors

Knauf JA, *et al.*, J Clin Invest 2018; 128:4086-4097

Molecular and Cellular Pathobiology

Cancer Research

The miR-146b-3p/PAX8/NIS Regulatory Circuit Modulates the Differentiation Phenotype and Function of Thyroid Cells during Carcinogenesis

Garcilaso Riesco-Eizaguirre[1,2,3], León Wert-Lamas[1], Javier Perales-Patón[1,4], Ana Sastre-Perona[1], Lara P. Fernández[1], and Pilar Santisteban[1]

https://doi.org/10.1038/s41388-017-0088-9

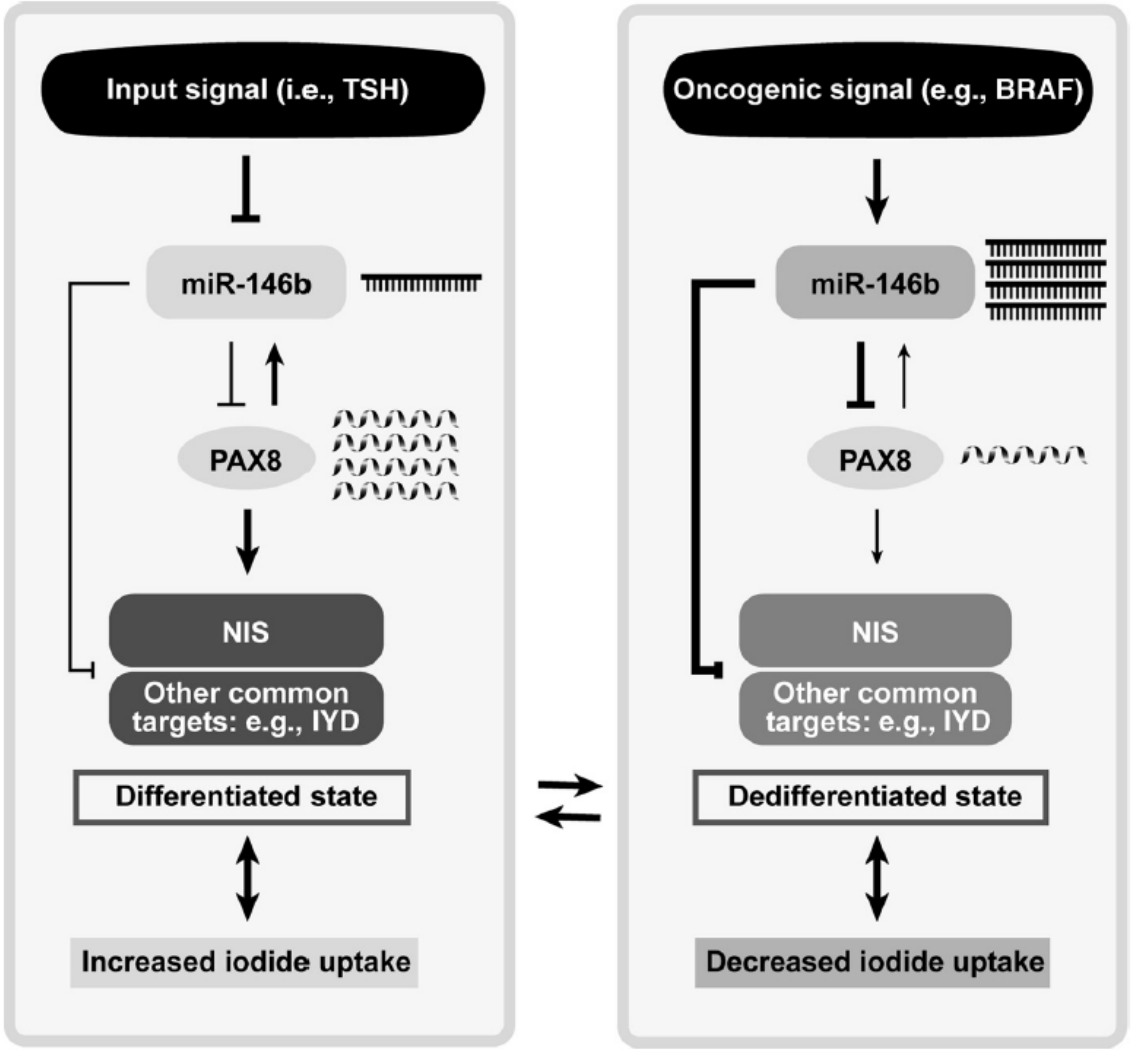
ARTICLE

MicroRNA-146b promotes PI3K/AKT pathway hyperactivation and thyroid cancer progression by targeting PTEN

Julia Ramírez-Moya[1] · León Wert-Lamas[1] · Pilar Santisteban[1,2]

Riesco-Eizaguirre G, *et al.*, Cancer Res 2015; 75:4119-4130
Ramirez-Moya J, *et al.*, Oncogene 2018; 37:3369-3383

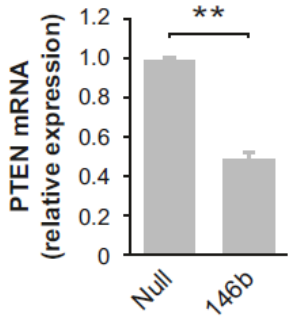
miR-146b – a novel target for thyroid cancer therapy?

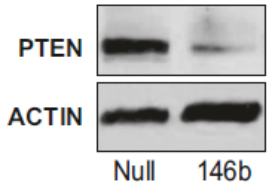


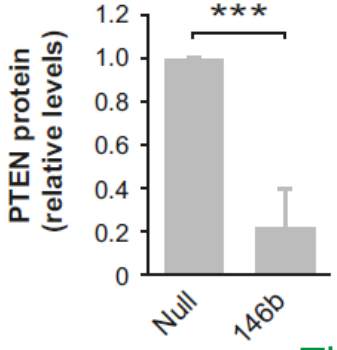
Riesco-Eizaguirre G, *et al.*, Cancer Res 2015; 75:4119-4130

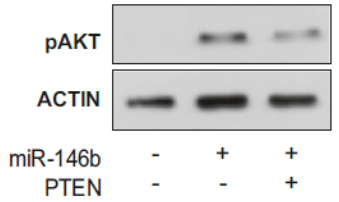
miR-146b – a novel target for thyroid cancer therapy?

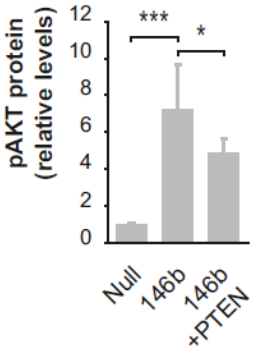
Modulation of the PI3K signaling by miR-146b via PTEN silencing

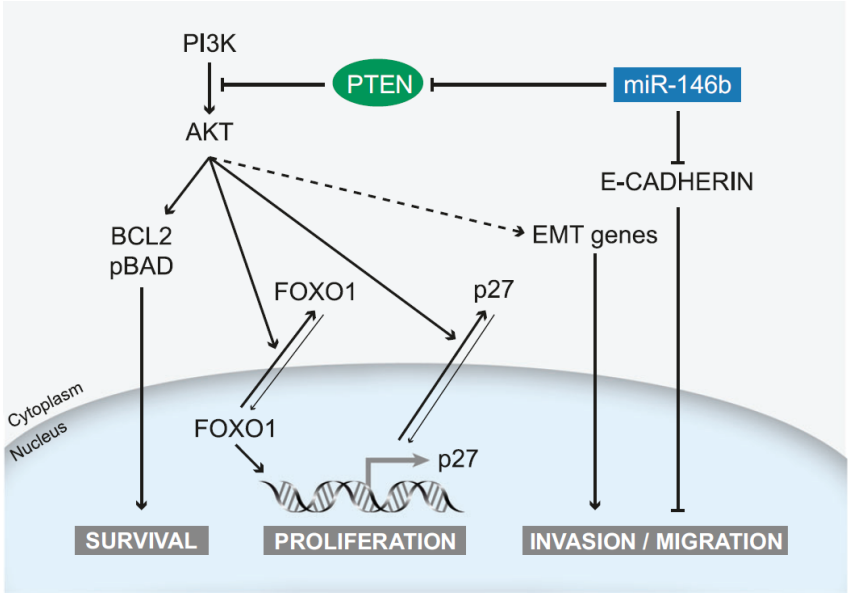




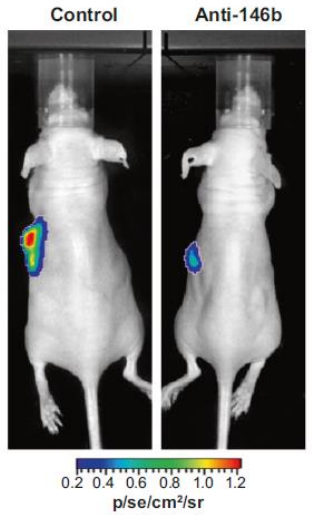


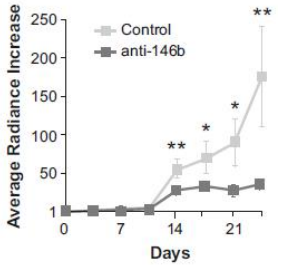


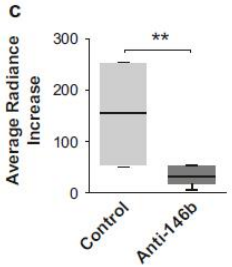




Therapeutic efficacy of the hsa-miR-146b-5p mir-Vana® miRNA inhibitor







Ramirez-Moya J, *et al.*, Oncogene 2018; 37:3369-3383

nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-018-03033-1 OPEN

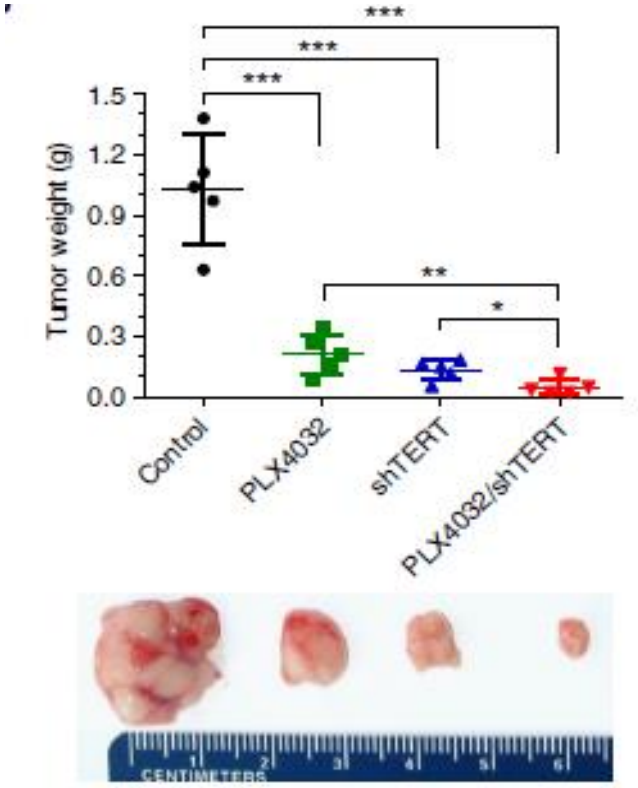
Regulation of mutant *TERT* by BRAF V600E/MAP kinase pathway through FOS/*GABP* in human cancer

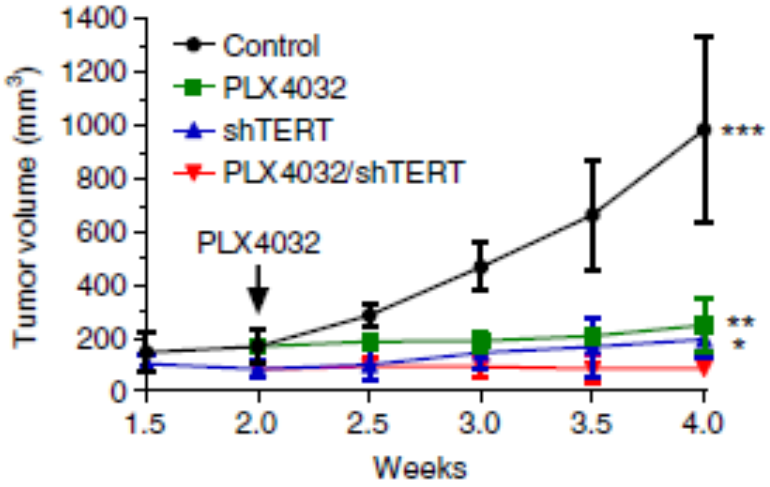
Rengyun Liu[1], Tao Zhang[1], Guangwu Zhu[1] & Mingzhao Xing[1]

Liu R, *et al.*, Nature Commun 2018; 9:579-592

Oncogene duet
mutant TERT & BRAF V600E

- Oncogene duet of BRAF V600E and TERT promoter mutations is a fundamental genetic background cooperatively driving progression/aggressiveness of cancers, i.e. PTC



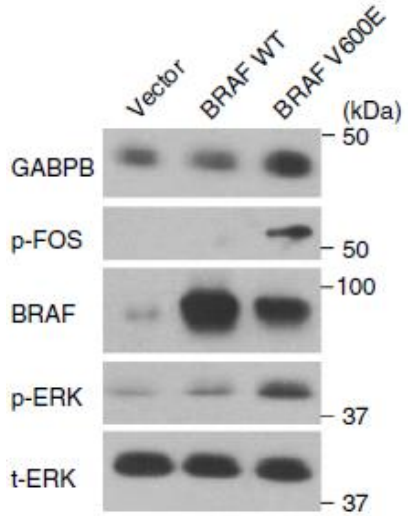


➡ Molecular mechanism for synergistic oncogenic effect?

Liu R, *et al.*, Nature Commun 2018; 9:579-592

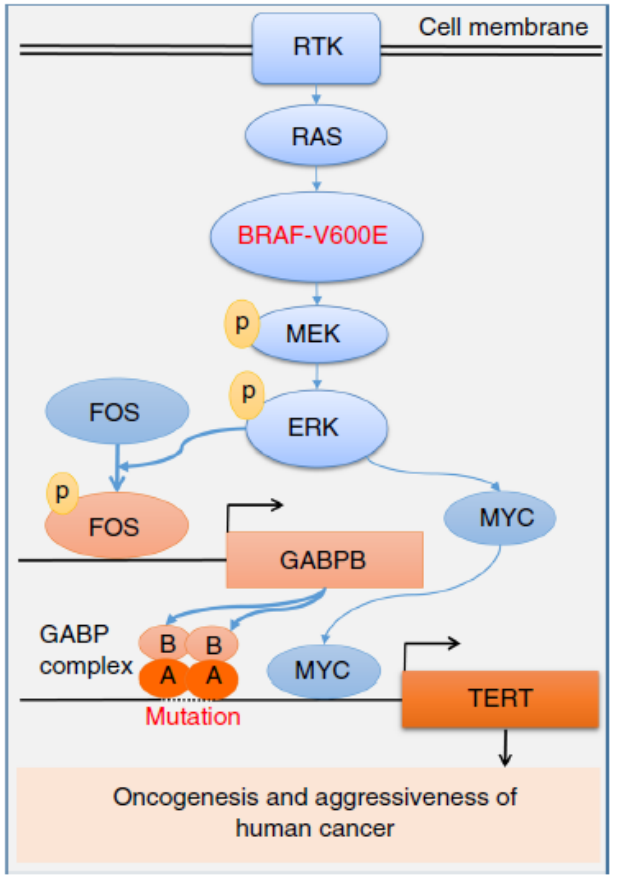
Oncogene duet
mutant TERT & BRAF V600E

Upregulation of GABPB by BRAF V600E



GABPB complex a known activator of mut TERT promoter

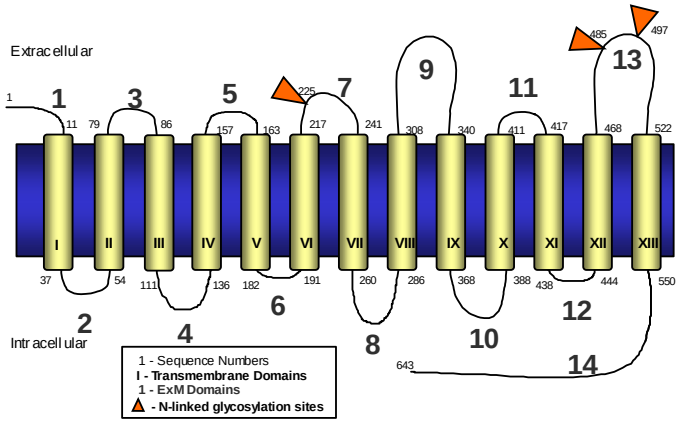
FOS transcription factor of the GABPB gene



➡ BRAF/MAPK-induced FOS activation, a transcription factor activating GABPB promoter, a known activator of mut TERT promoter plays a key role in bridging the 2 oncogenes cooperatively driving oncogenesis

Liu R, *et al.*, Nature Commun 2018; 9:579-592

The sodium iodide symporter NIS



SCIENTIFIC REPORTS

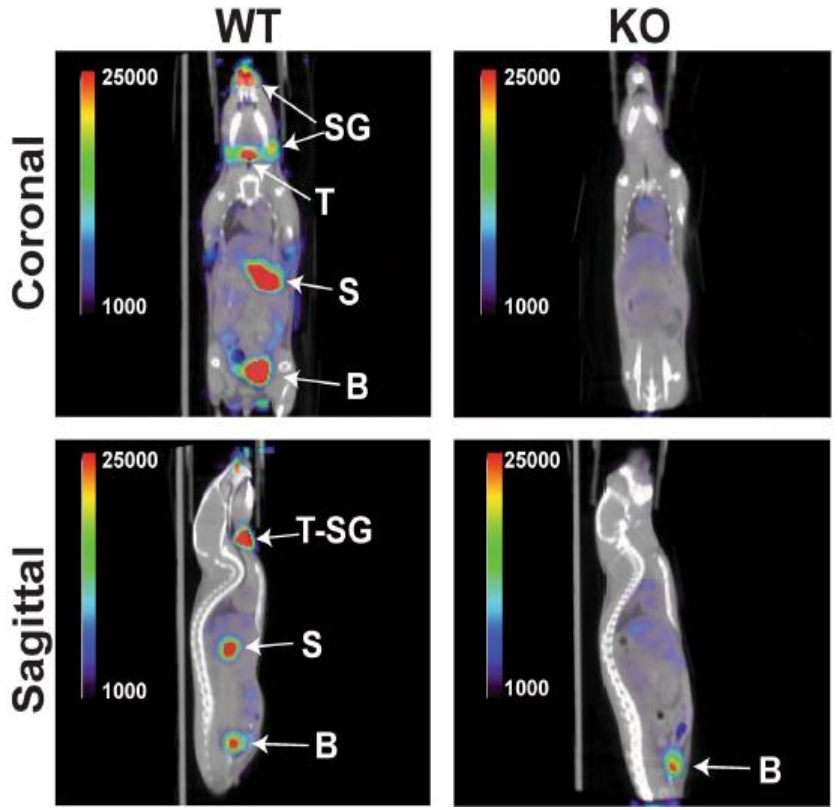
OPEN

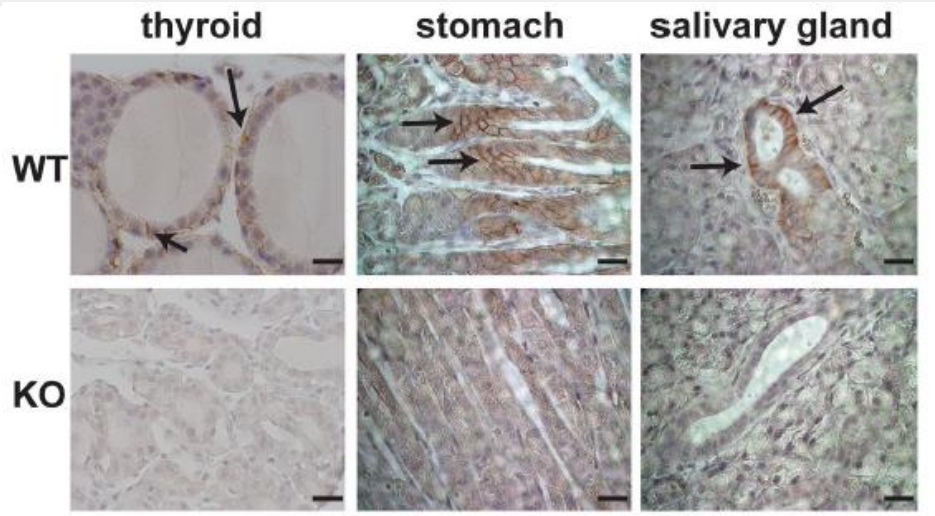
An extremely high dietary iodide supply forestalls severe hypothyroidism in Na^+/I^- symporter (NIS) knockout mice

Giuseppe Ferrandino[1], Rachel R. Kaspari[1], Andrea Reyna-Neyra[1], Nabil E. Boutagy[2], Albert J. Sinusas[2,3] & Nancy Carrasco[1]

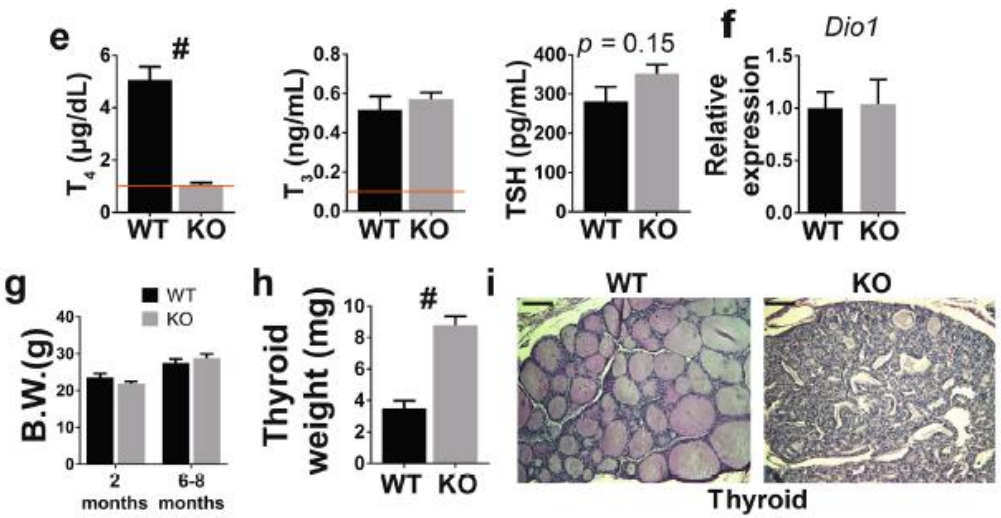
Ferrandino G, *et al.*, Sci Rep 2017; 7:5329-5340

NIS knockout mouse model





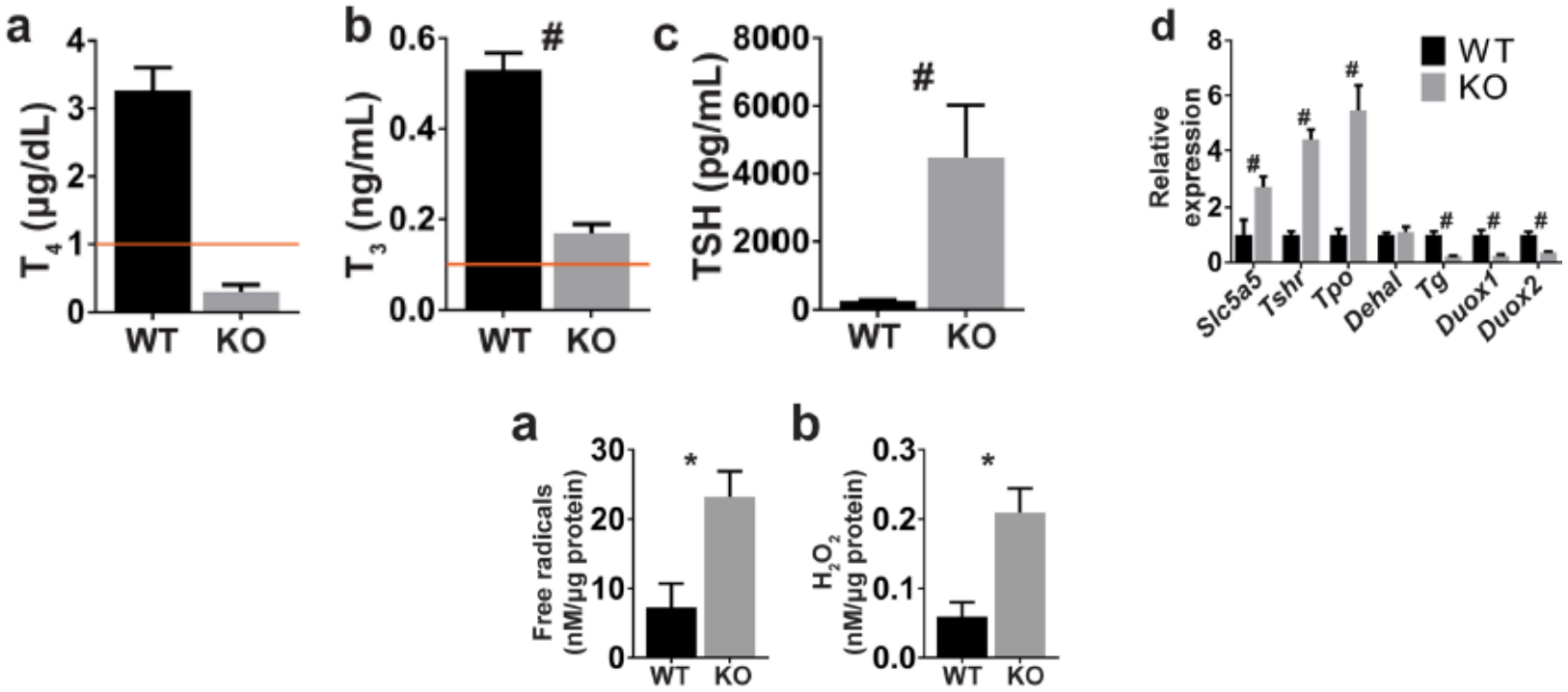
Standard chow diet (6 µg I^-/g)



Ferrandino G, *et al.*, Sci Rep 2017; 7:5329-5340

NIS knockout mouse model

Minimal iodide diet (0.15 µg I^-/g)



- Thyroid hormone is synthesized in NIS KO mice as long as I^- supply is sufficient to enter the thyroid most likely by diffusion via non-specific routes driven by a concentration gradient
- I^- gradient (serum/thyroid) is maintained by upregulating genes involved in I^- organification
- Enhanced oxidative environment in the thyroid (adaptive response)

Ferrandino G, *et al.*, Sci Rep 2017; 7:5329-5340

Research Article

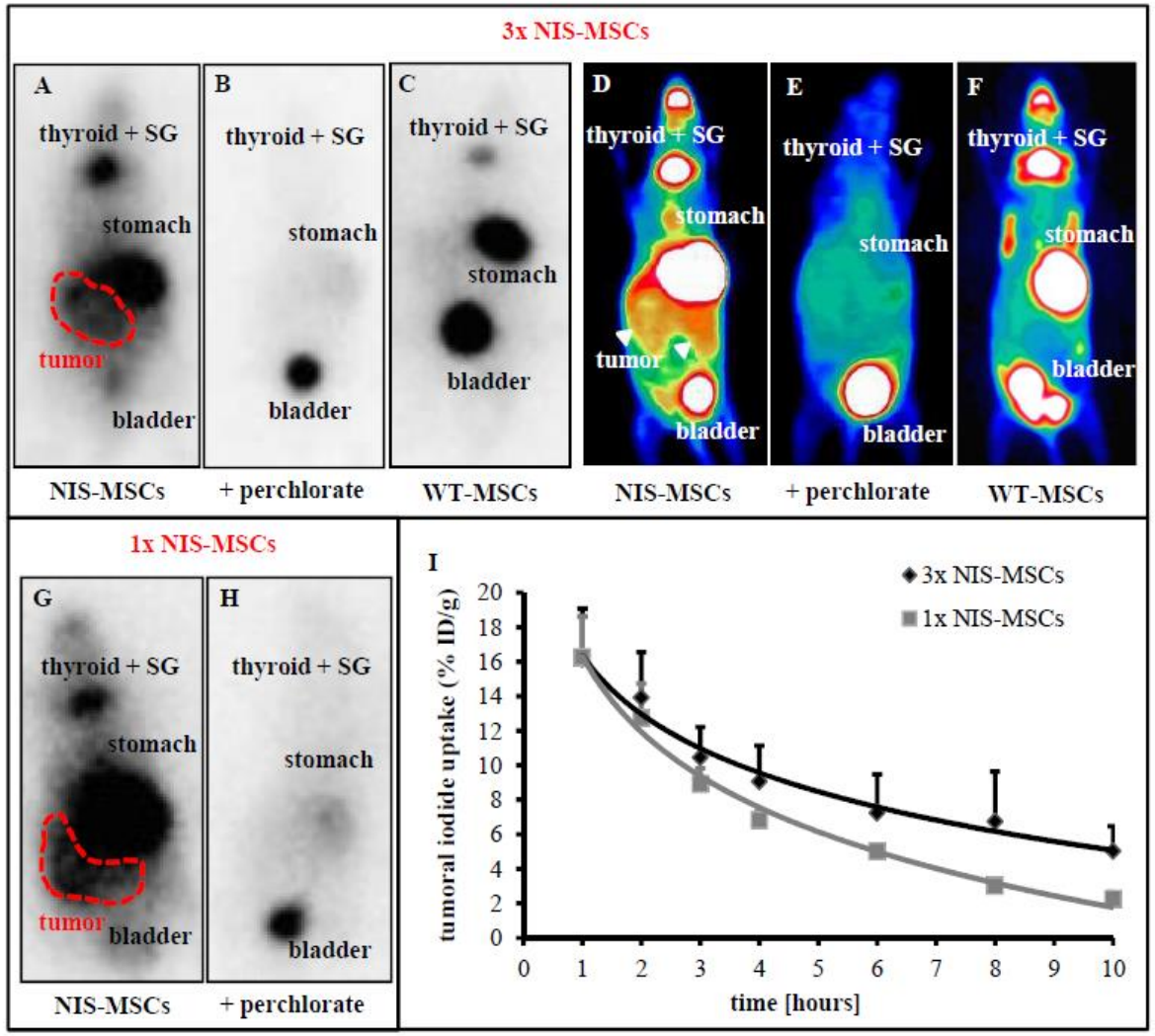
Molecular Cancer Research

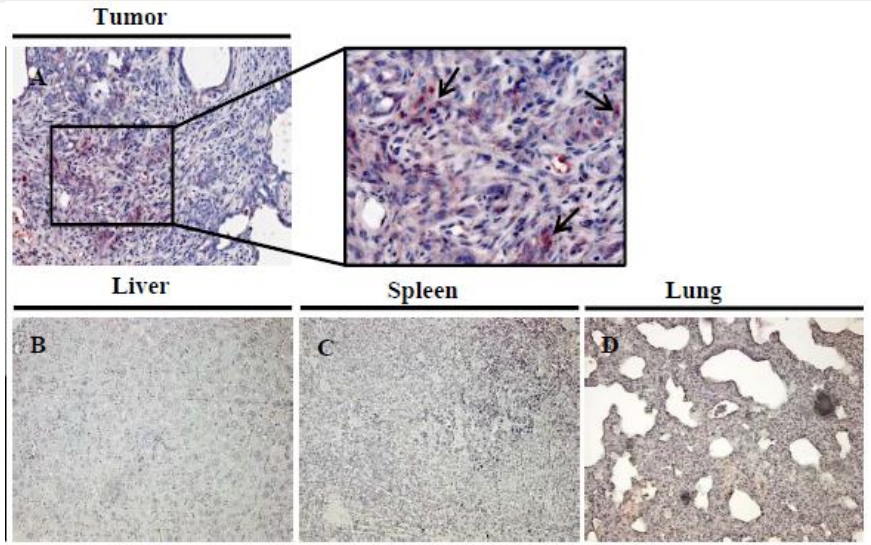
A Novel Approach for Image-Guided ^{131}I Therapy of Pancreatic Ductal Adenocarcinoma Using Mesenchymal Stem Cell-Mediated NIS Gene Delivery

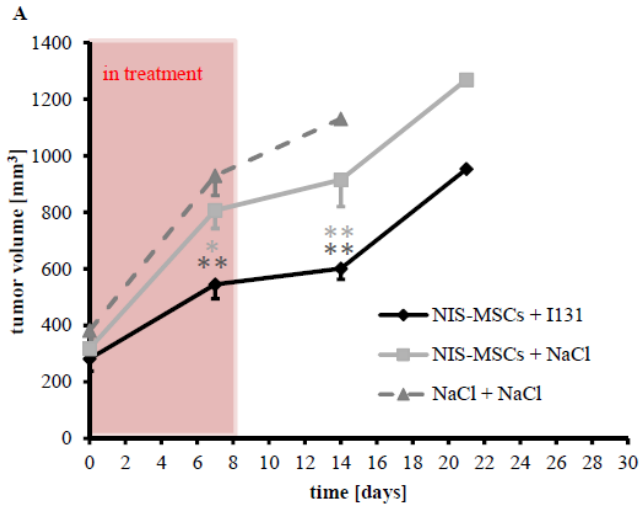
Christina Schug[1], Aayush Gupta[2], Sarah Urnauer[1], Katja Steiger[3], Phyllis Fung-Yi Cheung[4,5], Christian Neander[4,5], Konstantinos Savvatakis[4,5], Kathrin A. Schmohl[1], Marija Trajkovic-Arsic[4,5], Nathalie Schwenk[1], Markus Schwaiger[6], Peter J. Nelson[7], Jens T. Siveke[2,4,5], and Christine Spitzweg[1]

Schug C, *et al.*, Mol Cancer Res 2018; in press

NIS gene therapy in pancreatic cancer





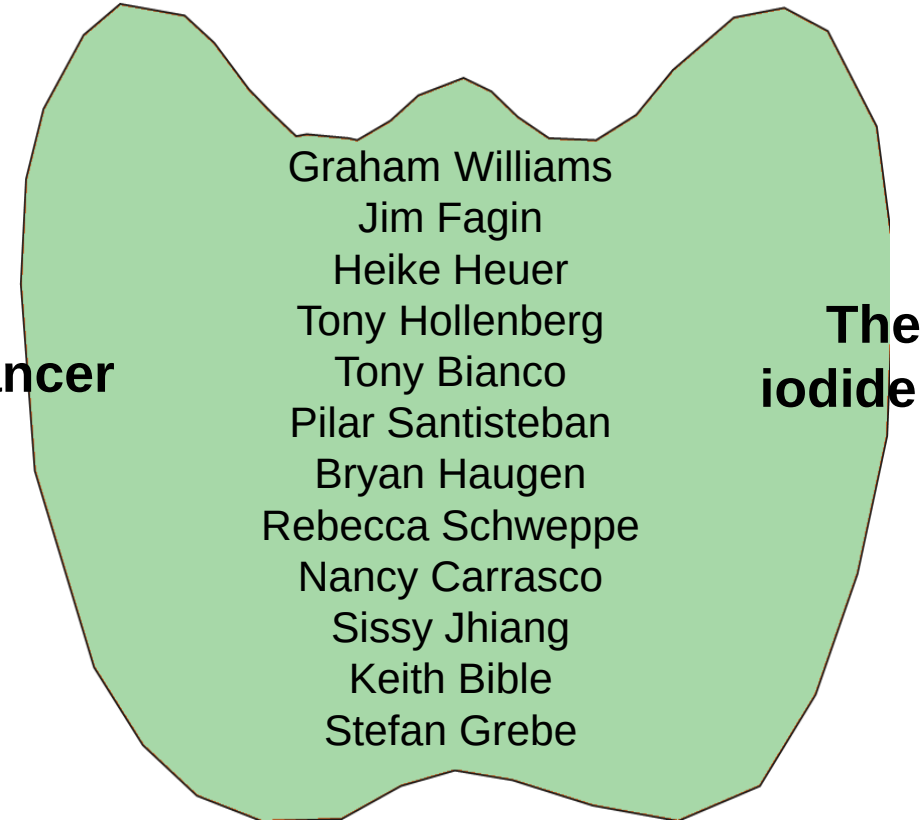


Schug C, *et al.*, Mol Cancer Res 2018; in press

Special Thanks

Thyroid hormone & Aging
Thyroid hormone & Food Intake

Thyroid cancer



The sodium iodide symporter NIS

Non-classical thyroid hormone action
Novel thyroid hormone targets