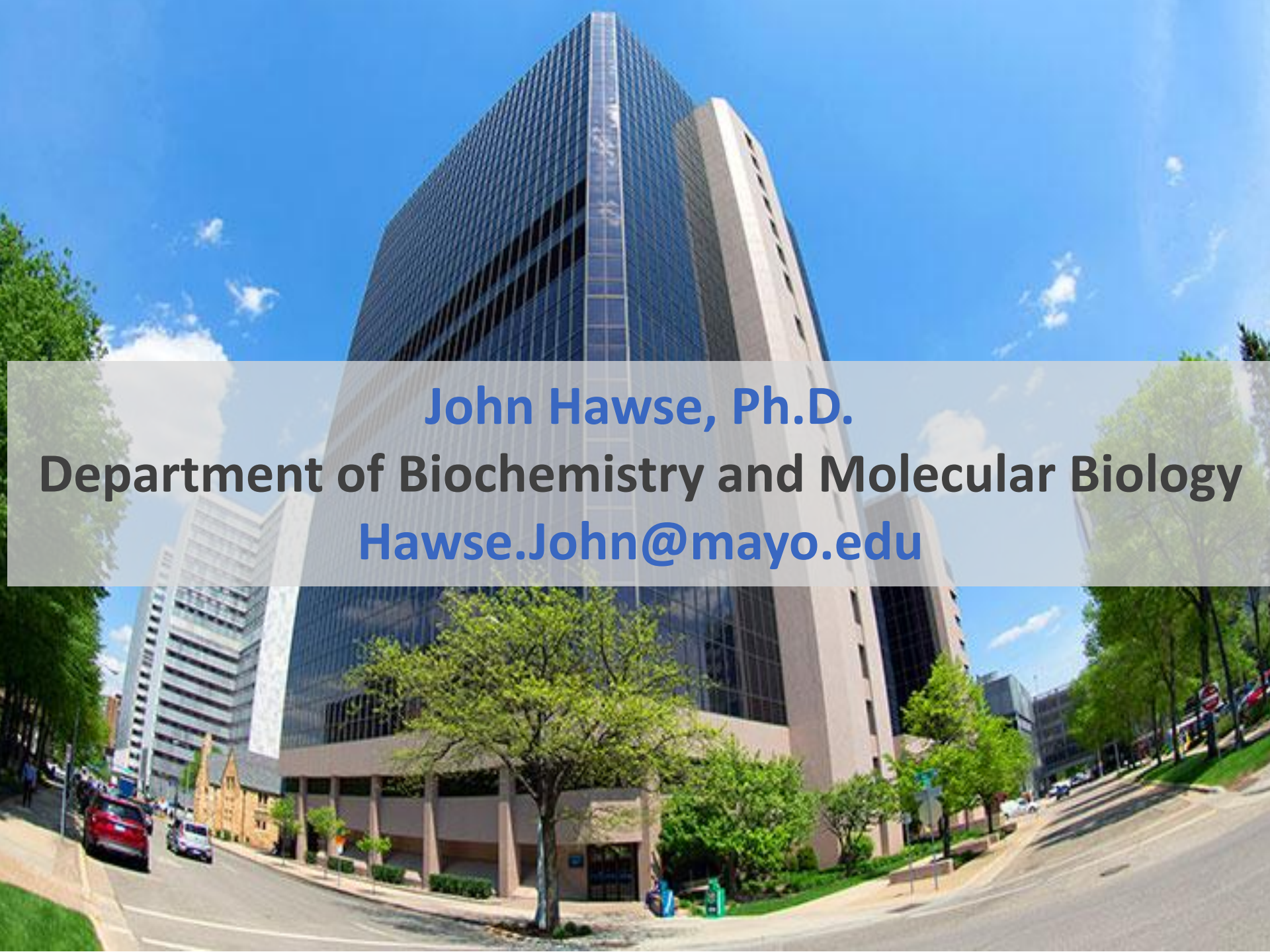


John Hawse, Ph.D.
Department of Biochemistry and Molecular Biology
Hawse.John@mayo.edu

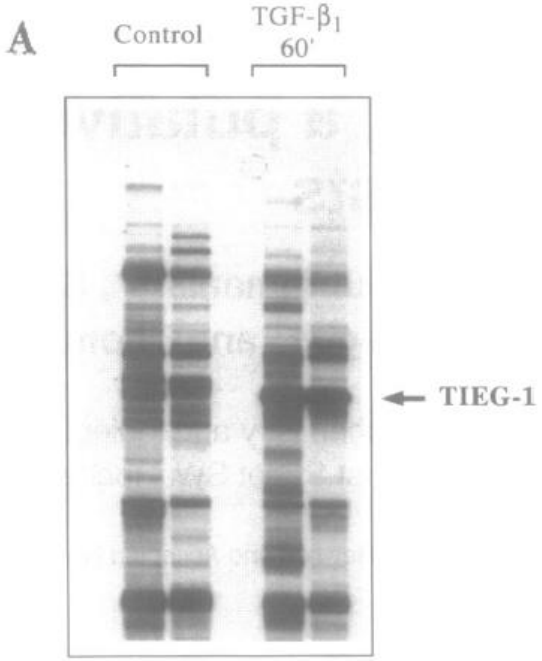
Discovery of TIEG/KLF10 in Osteoblast Cells

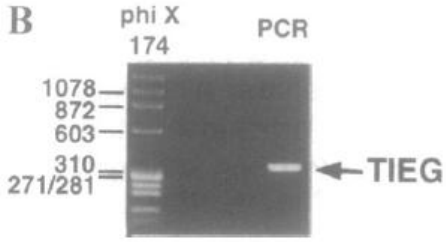
Nucleic Acids Research, 1995, Vol. 23, No. 23 ***4907–4912***

Identification of a novel TGF-β-regulated gene encoding a putative zinc finger protein in human osteoblasts

Malayannan Subramaniam*, Steven A. Harris, Merry Jo Oursler, Kay Rasmussen, B. Lawrence Riggs[1] and Thomas C. Spelsberg

Department of Biochemistry and Molecular Biology and [1]Endocrine Research Laboratory, Mayo Clinic and Foundation, 200 First Street SW, Rochester, MN 55905, USA





Impact of TIEG-Related Projects at Mayo Clinic

- **Have secured over 7 million dollars in funding from NIH and Mayo Clinic**

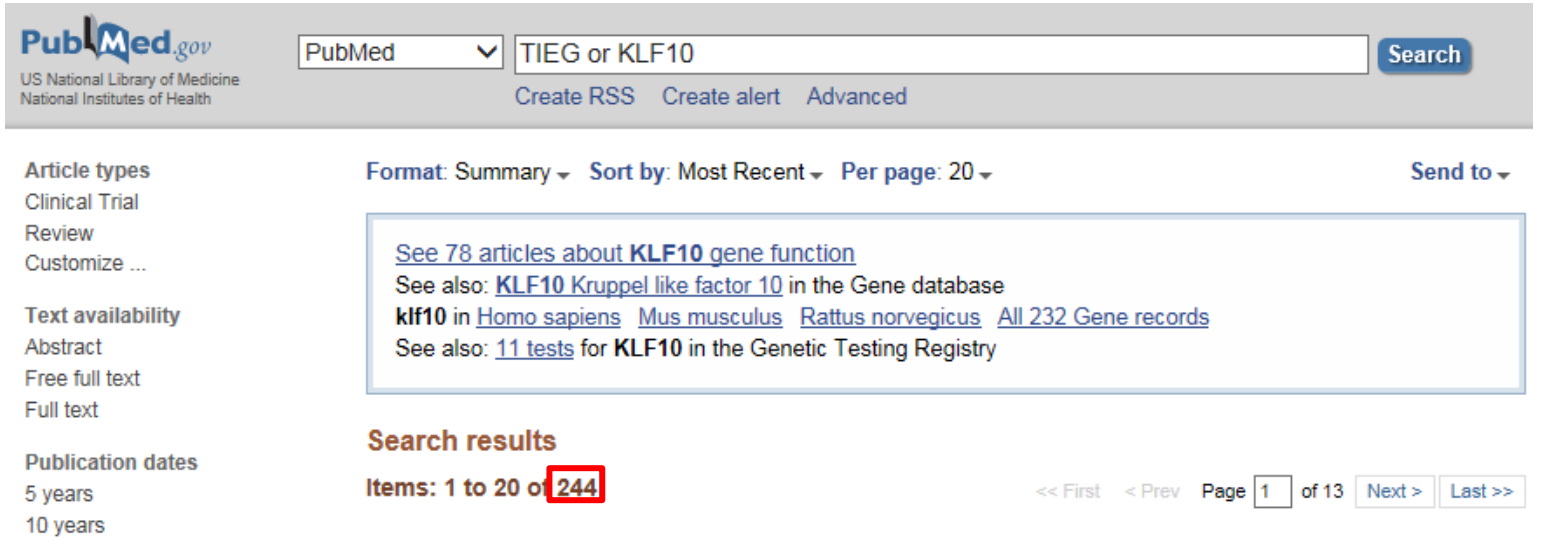
NIH National Institutes of Health

NIH NIH National Institute of Diabetes and Digestive and Kidney Diseases

National Institute of Dental and Craniofacial Research

MAYO CLINIC

- **Scientific discoveries detailed in 244 manuscripts to date**



Impact of TIEG-Related Projects at Mayo Clinic

✓ 10 young investigator awards at international meetings

ASBMR®
The American Society for Bone and Mineral Research

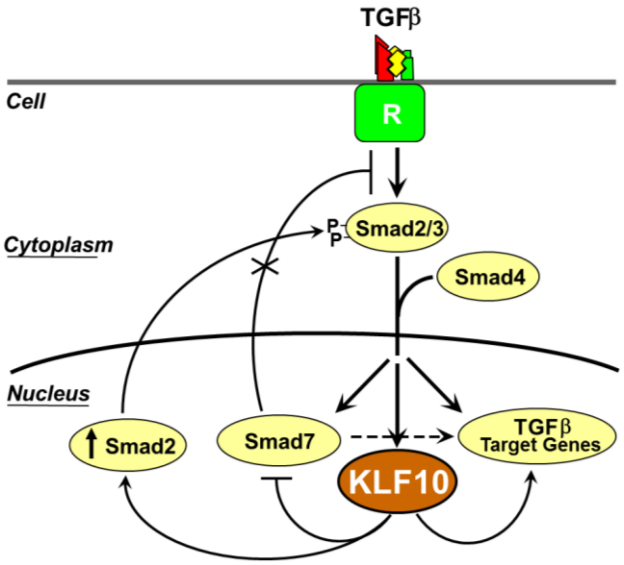
ENDOCRINE SOCIETY
Hormone Science to Health

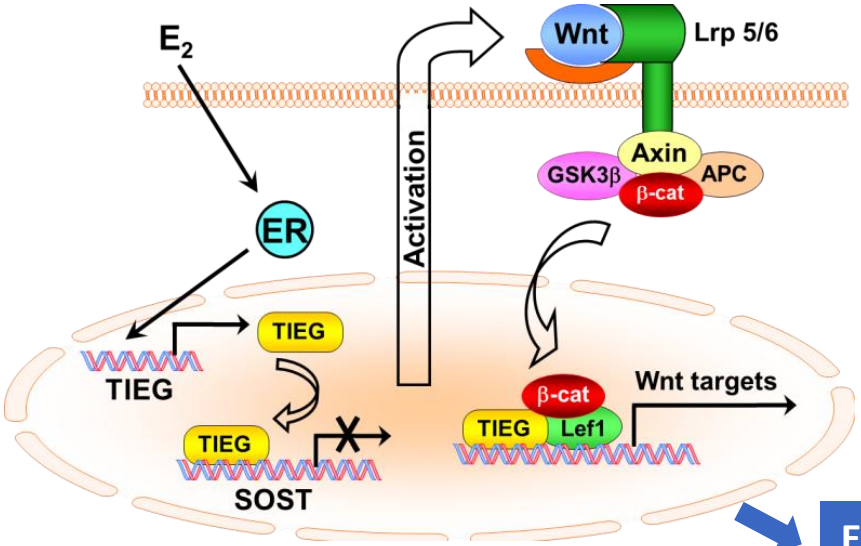
ascb
an international forum for cell biology

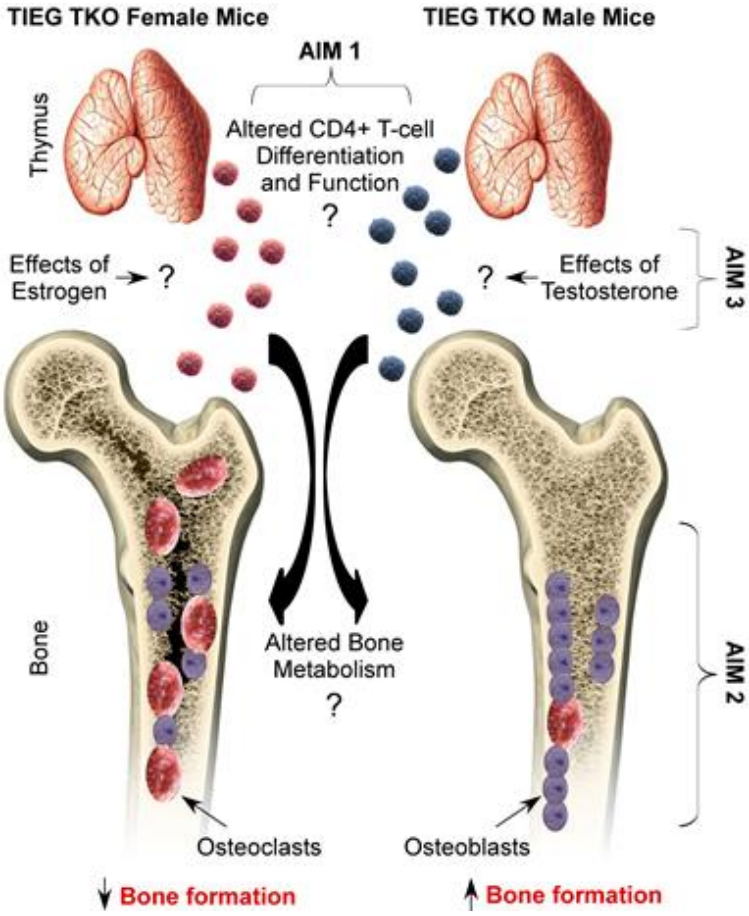
✓ 1 training grant for promising scientist

✓ 5 patent applications

Biological Functions of TIEG/KLF10



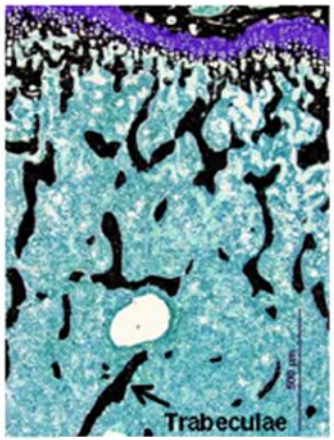




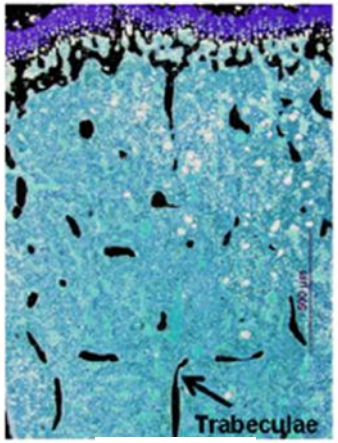
Enhanced Bone Formation

M. Subramaniam et al., NAR, 1995

TIEG and Osteoporosis

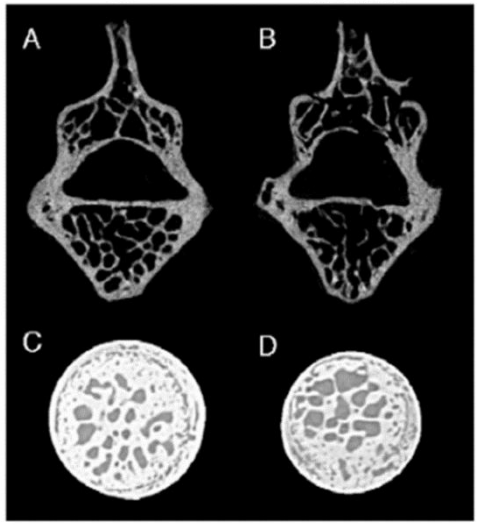


Wild Type



KO TIEG

Wild Type KO TIEG



ORIGINAL ARTICLE

JBMR

Candidate Gene Analysis of Femoral Neck Trabecular and Cortical Volumetric Bone Mineral Density in Older Men

Laura M Yerges,[1] Lambertus Klei,[2] Jane A Cauley,[1] Kathryn Roeder,[3] Candace M Kammerer,[4] Kristine E Ensrud,[5] Cara S Nestlerode,[1] Cora Lewis,[6] Thomas F Lang,[7] Elizabeth Barrett-Connor,[8] Susan P Moffett,[1] Andrew R Hoffman,[9] Robert E Ferrell,[4] Eric S Orwoll,[10] and Joseph M Zmuda[1,4] for the Osteoporotic Fractures in Men (MrOS) Study Group

Contents lists available at ScienceDirect

Bone

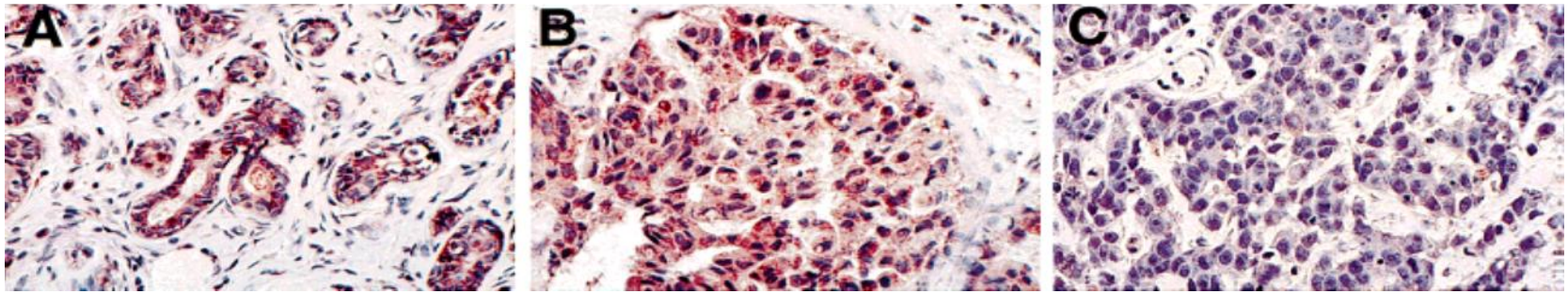
journal homepage: www.elsevier.com/locate/bone

Gene expression profile of the bone microenvironment in human fragility fracture bone

B. Hopwood [a,e], A. Tsykin [b], D.M. Findlay [c,e], N.L. Fazzalari [a,d,e,*]

TIEG and Cancer

Normal Breast | Ductal Carcinoma In Situ | Invasive Carcinoma



Journal of Cellular Biochemistry 68:226–236 (1998)

Tissue, Cell Type, and Breast Cancer Stage-Specific Expression of a TGF-β Inducible Early Transcription Factor Gene

M. Subramaniam,[1*] T.E. Hefferan,[1] K. Tau,[1] D. Peus,[2] M. Pittelkow,[2] S. Jalal,[3] B.L. Riggs,[4] P. Roche,[5] and T.C. Spelsberg[1]

[1]Department of Biochemistry and Molecular Biology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55905
[2]Dermatology Research, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55905
[3]Cytogenetics Laboratory, Department of Laboratory Medicine and Pathology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55905
[4]Endocrine Research, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55905
[5]Laboratory Medicine and Pathology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55905

Breast Cancer Research and Treatment **86:** 75–88, 2004.

Report

Differential gene expression of TGFβ inducible early gene (TIEG), Smad7, Smad2 and Bard1 in normal and malignant breast tissue

Monica M. Reinholz[1,3], Ming-Wen An[2], Steven A. Johnsen[3], Malayannan Subramaniam[3], Vera J. Suman[2], James N. Ingle[4], Patrick C. Roche[1,5], and Thomas C. Spelsberg[3]

[1]*Division of Experimental Pathology,* [2]*Division of Biostatistics,* [3]*Departments of Biochemistry and Molecular Biology,* [4]*Department of Oncology, Mayo Clinic College of Medicine, Rochester, MN,* [5]*Present Address: Department of Scientific and Clinical Affairs, Ventana Medical Systems, Inc., Tucson, AZ, USA*

Oncogene (2017) **36,** 5532–5543

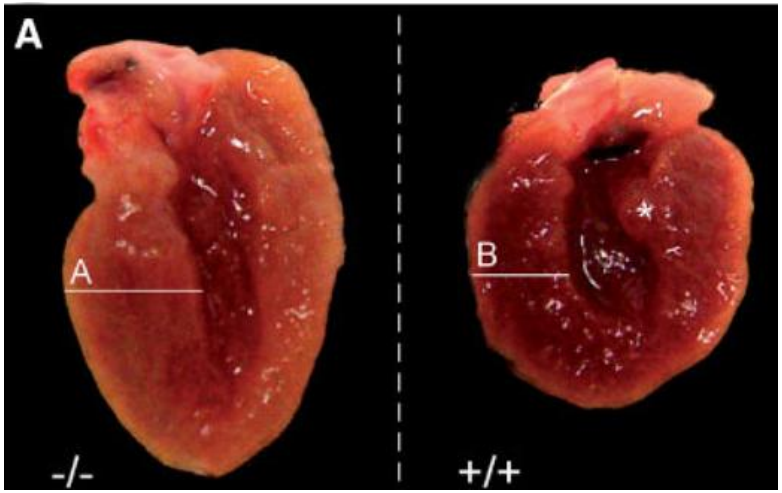
www.nature.com/onc

ORIGINAL ARTICLE

KLF10 loss in the pancreas provokes activation of SDF-1 and induces distant metastases of pancreatic ductal adenocarcinoma in the $Kras^{G12D}$ $p53^{flox/flox}$ model

C-C Weng[1], JR Hawse[2], M Subramaniam[2], VHS Chang[3], WCY Yu[4], W-C Hung[4,5], L-T Chen[4,6,8] and K-H Cheng[1,4,7,8]

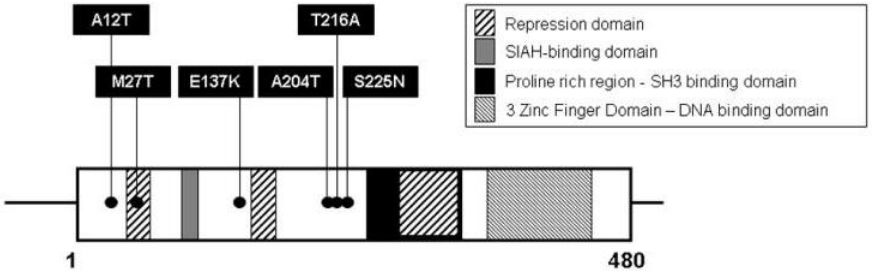
TIEG and Cardiomyopathies



Published in final edited form as:
J Cell Biochem. 2007 February 1; 100(2): 315–325. doi:10.1002/jcb.21049.

TGFβ Inducible Early Gene-1 (*TIEG1*) and Cardiac Hypertrophy: Discovery and Characterization of a Novel Signaling Pathway

Nalini M. Rajamannan[1,*], Malayannan Subramaniam[2], Theodore P. Abraham[3], Vlad C. Vasile[4], Michael J. Ackerman[3,4,5], David G. Monroe[2], Teng-Leong Chew[6], and Thomas C. Spelsberg[2]

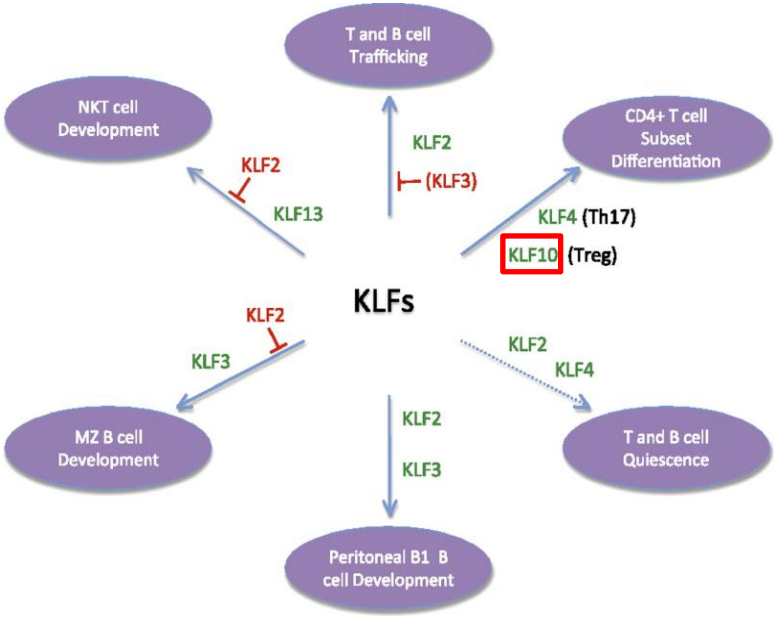


Published in final edited form as:
J Cell Biochem. 2012 June ; 113(6): 1896–1903. doi:10.1002/jcb.24058.

TGFβ-Inducible Early Gene-1 (*TIEG1*) Mutations in Hypertrophic Cardiomyopathy

J. Martijn Bos, MD, PhD[1], Malayannan Subramaniam, PhD[2], John R. Hawse, PhD[2], I. Christiaans, MD, PhD[3,4], Nalini M Rajamannan, MD[5], Joseph J. Maleszewski, MD[6], William D. Edwards, MD[6], Arthur A.M. Wilde, MD, PhD[4], Thomas C. Spelsberg, PhD[2], and Michael J. Ackerman, MD, PhD[1,7,8]

TIEG and Immunology



Published in final edited form as:
Nat Immunol. 2008 March ; 9(3): 245–253. doi:10.1038/niXXXX.

The E3 ubiquitin ligase Itch regulates expression of transcription factor Foxp3 and airway inflammation by enhancing the function of transcription factor TIEG1

K Venuprasad[1], Haining Huang[1], Yousuke Harada[1], Chris Elly[1], Malayannan Subramaniam[2], Thomas Spelsberg[2], Jin Su[1], and Yun-Cai Liu[1]

1 *Division of Cell Biology, La Jolla Institute for Allergy and Immunology, La Jolla, California 92037, USA*

2 *Mayo Clinic and Foundation, Rochester, Minnesota 55905, USA*

Am J Physiol Gastrointest Liver Physiol. 2015 Dec 1; 309(11): G900–G909.
Published online 2015 Oct 15. doi: 10.1152/ajpgi.00309.2015: 10.1152/ajpgi.00309.2015

PMCID: PMC4669350
PMID: 26472224

Krüppel-like factor KLF10 deficiency predisposes to colitis through colonic macrophage dysregulation

Konstantinos A. Papadakis,[1] James Krempski,[1] Phyllis Svingen,[1] Yuning Xiong,[1] Olga F. Sarmento,[1] Gwen A. Lomberk,[2] Raul A. Urrutia,[2] and William A. Faubion[1]

[1]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota; and
[2]Epigenetics and Chromatin Dynamics Laboratory, Departments of Medicine and Biochemistry and Molecular Biology, Epigenetic Translational Program, Center for Individualized Medicine, Mayo Clinic, Rochester, Minnesota

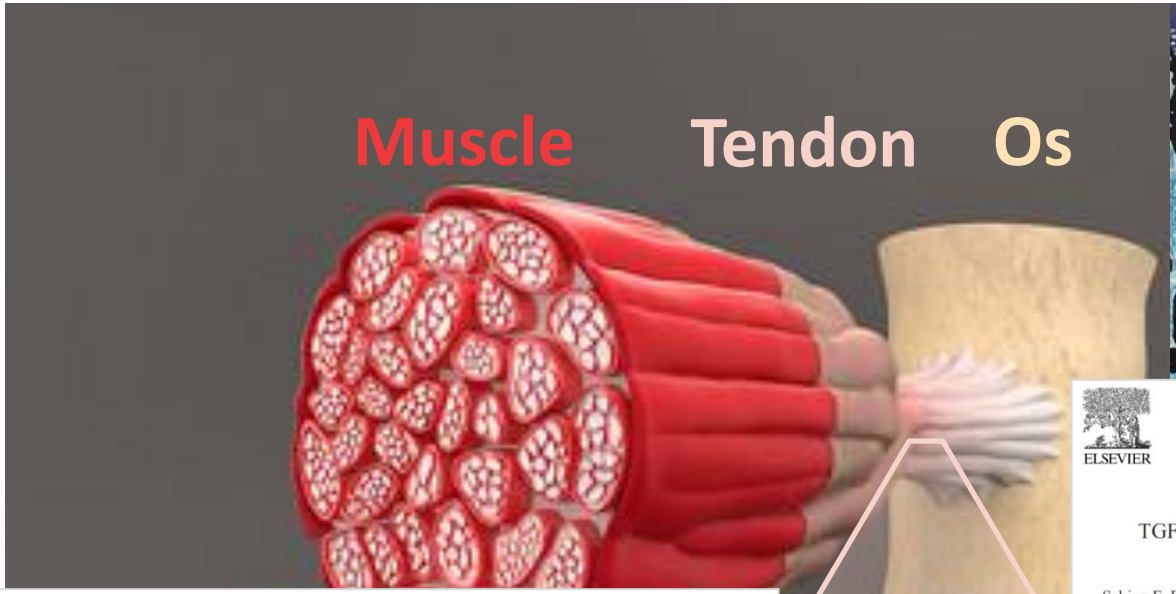
THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 284, NO. 37, pp. 24914–24924, September 11, 2009

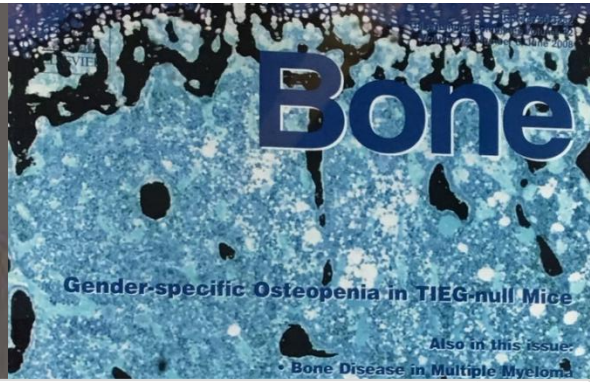
Kruppel-like Factor KLF10 Targets Transforming Growth Factor-β1 to Regulate CD4$^+$CD25$^-$ T Cells and T Regulatory Cells[*][S]

Received for publication, March 2, 2009, and in revised form, July 14, 2009 Published, JBC Papers in Press, July 14, 2009, DOI 10.1074/jbc.M109.000059

Zhuoxiao Cao[‡], Akm Khyrul Wara[‡1], Basak Icli[‡1], Xinghui Sun[‡], René R. S. Packard[‡], Fehim Esen[‡], Christopher J. Stapleton[‡5], Malayannan Subramaniam[¶], Karsten Kretschmer[‖], Irina Apostolou[‖], Harald von Boehmer[‖], Göran K. Hansson[**], Thomas C. Spelsberg[¶], Peter Libby[‡], and Mark W. Feinberg[‡2]

Role of TIEG in the musculoskeletal system





ELSEVIER

Bone 39 (2006) 1244–1251

BONE

www.elsevier.com/locate/bone

TGFβ inducible early gene-1 knockout mice display defects in bone strength and microarchitecture

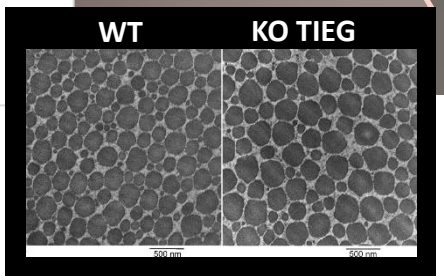
Sabine F. Bensamoun [a], John R. Hawse [b], Malayannan Subramaniam [b], Brice Ilharreborde [a], Armelle Bassillais [c], Claude L. Benhamou [c], Daniel G. Fraser [d], Merry J. Oursler [d], Peter C. Amadio [a], Kai-Nan An [a], Thomas C. Spelsberg [b,*]

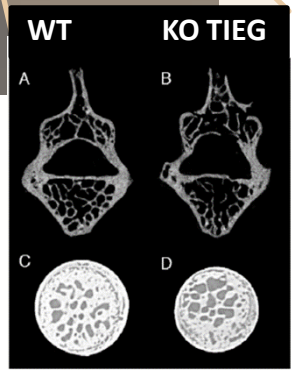
J Appl Physiol 101: 1419–1424, 2006.
First published June 22, 2006; doi:10.1152/japplphysiol.00800.2005.

Age-dependent changes in the mechanical properties of tail tendons in TGF-β inducible early gene-1 knockout mice

Sabine F. Bensamoun,[1] Tetsu Tsubone,[1] Malayannan Subramaniam,[2] John R. Hawse,[2] Emir Boumediene,[1] Thomas C. Spelsberg,[2] Kai-Nan An,[1] and Peter C. Amadio[1]
[1]*Biomechanics Laboratory, Department of Orthopedics, and* [2] *Department of Biochemistry and Molecular Biology, Mayo Clinic Rochester, Rochester, Minnesota*

Submitted 6 July 2005; accepted in final form 19 June 2006



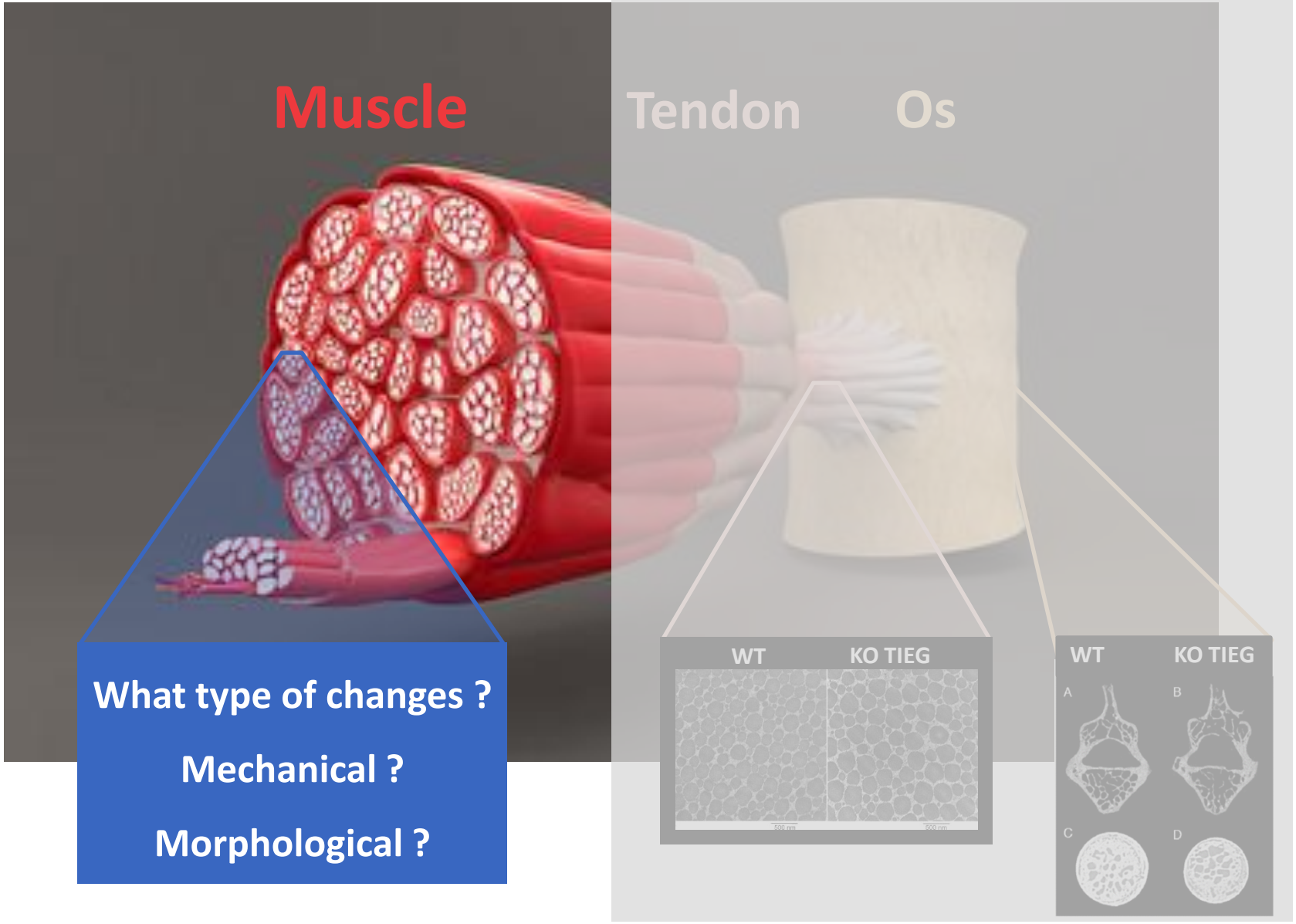


Published in final edited form as:
Exp Cell Res. 2011 July 15; 317(12): 1726–1735. doi:10.1016/j.yexcr.2011.05.007.

TIEG1-null tenocytes display age-dependent differences in their gene expression, adhesion, spreading and proliferation properties

Oualid Haddad[a], Laurie Gumez[a], John R. Hawse[b], Malayannan Subramaniam[b], Thomas C. Spelsberg[b], and Sabine F. Bensamoun[a,*]

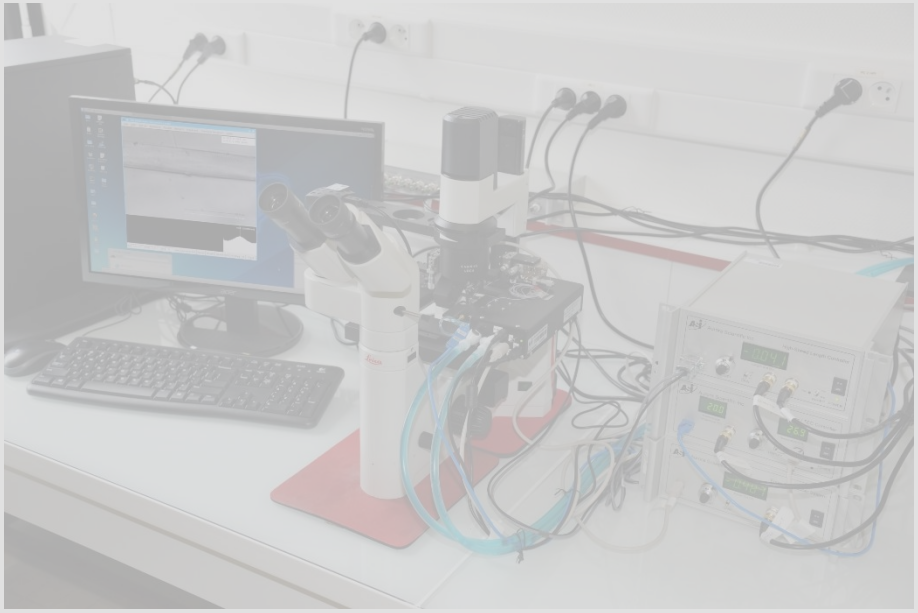
Role of TIEG in the Musculoskeletal System



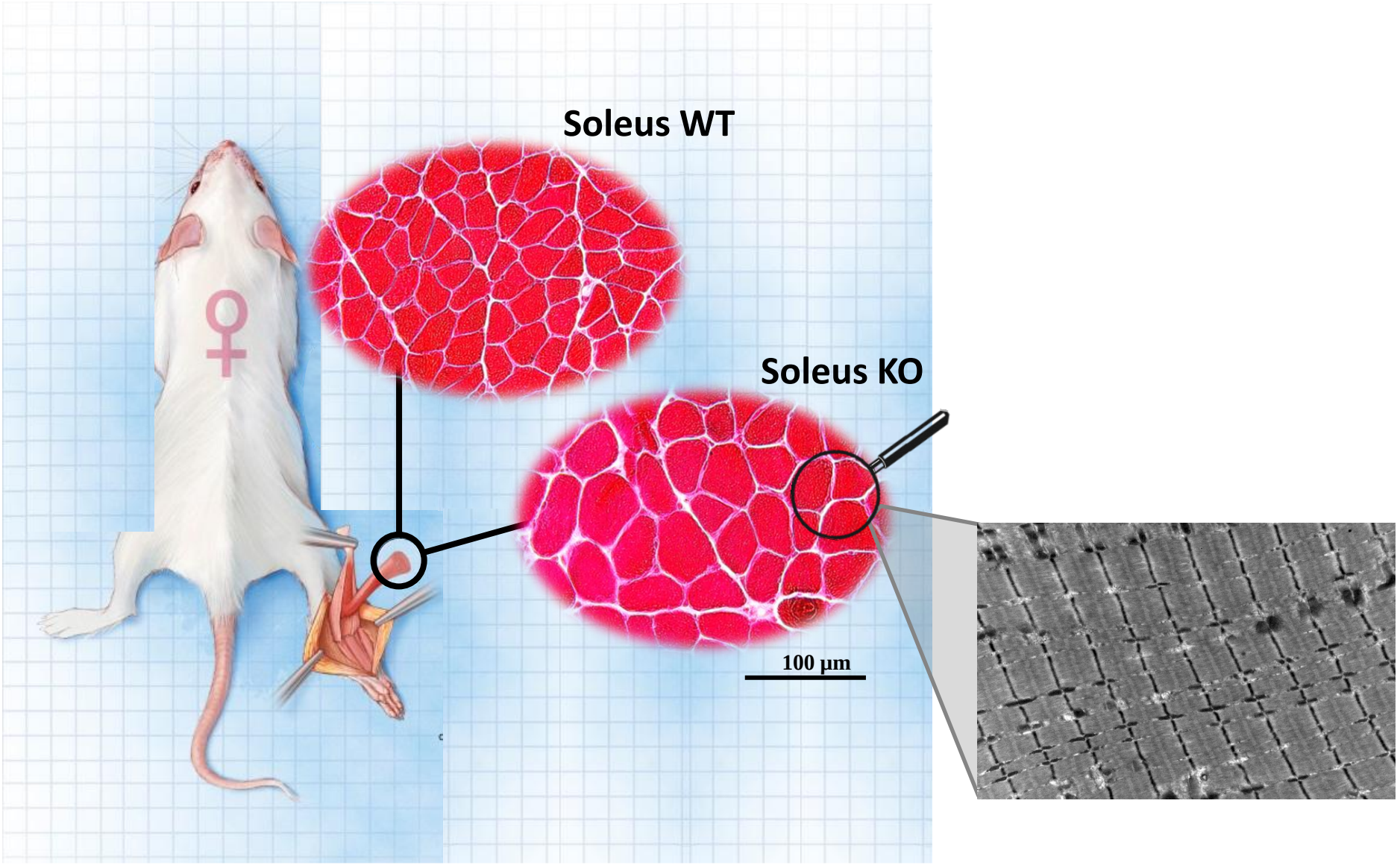
Role of TIEG in the Skeletal Muscle

Morphological analysis

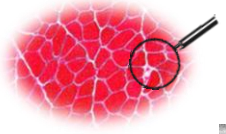
Functional analysis



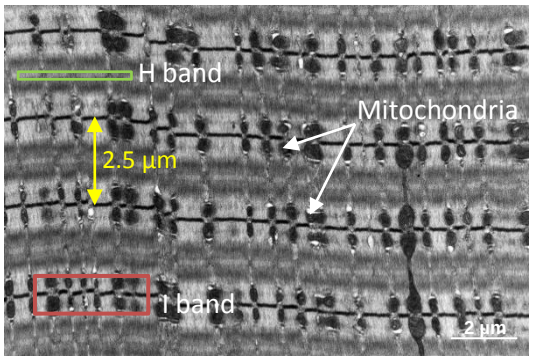
Deletion of TIEG Results in Muscle Fiber Hypertrophy

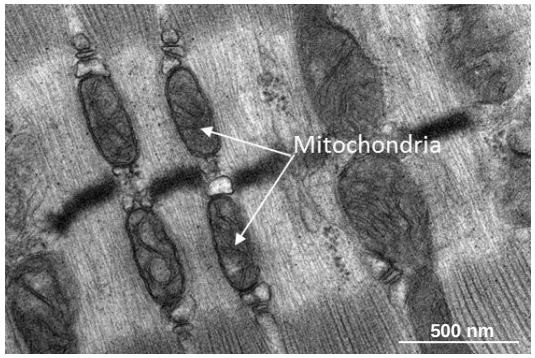


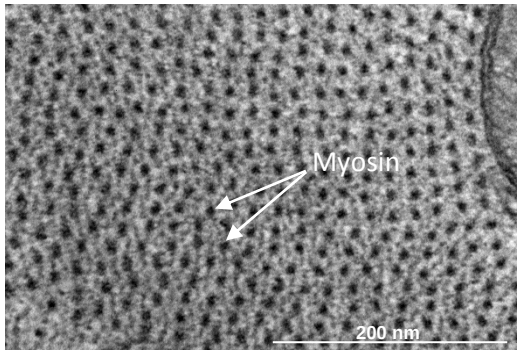
Deletion of TIEG leads to Disorganization of Muscle Ultrastructure



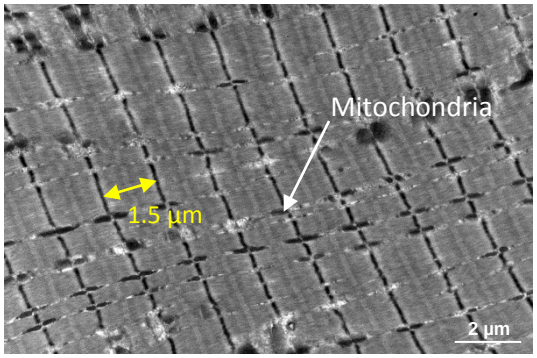
Soleus Control

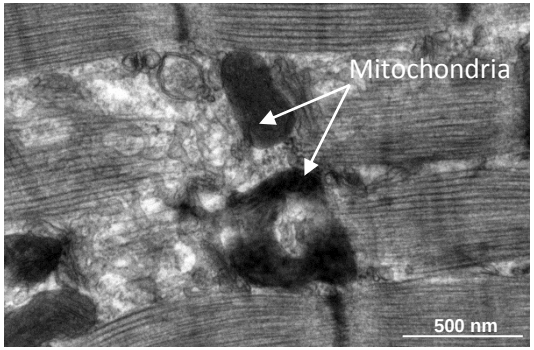


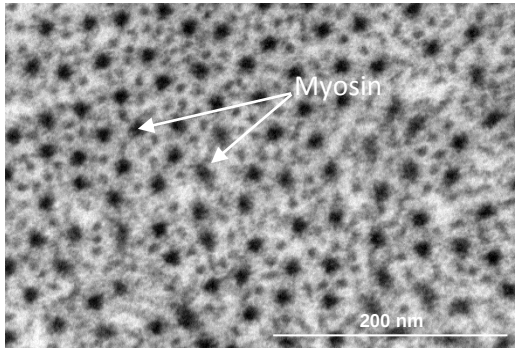




Soleus KO TIEG

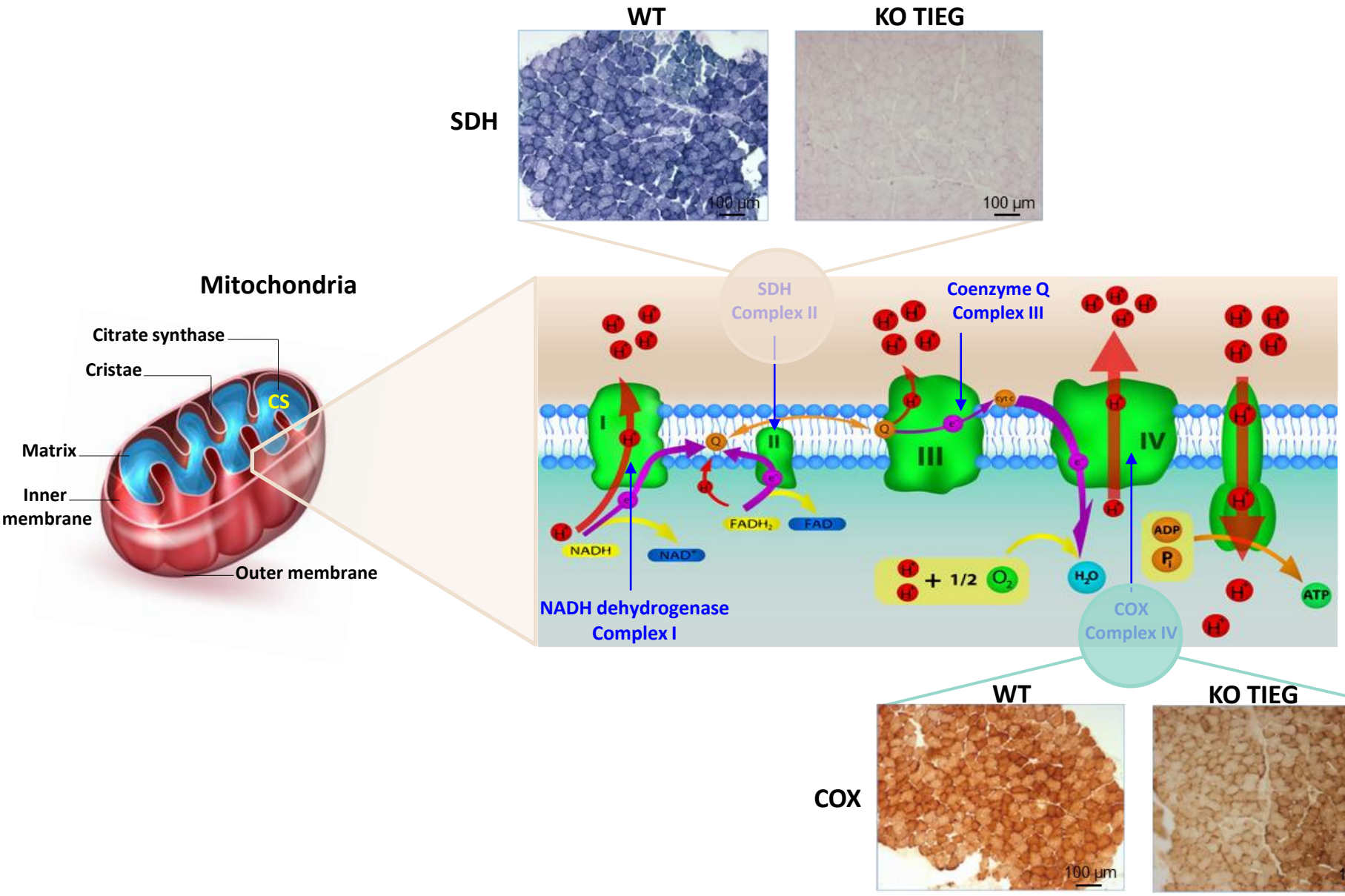




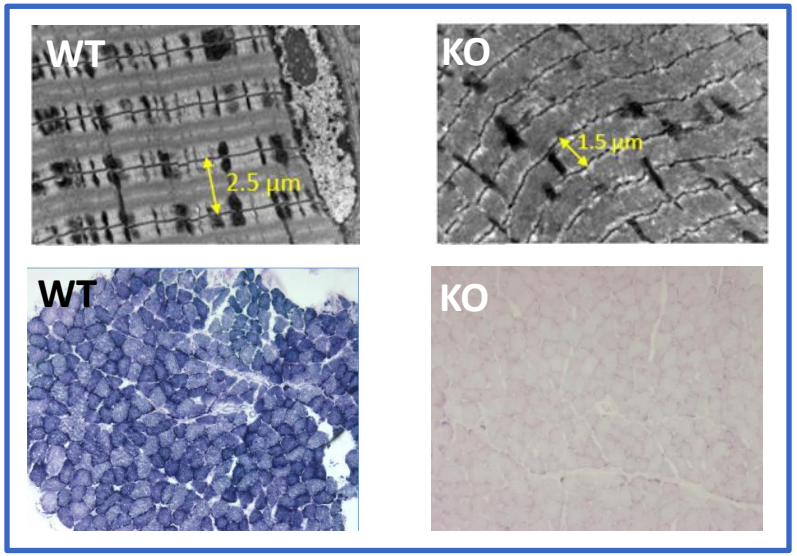


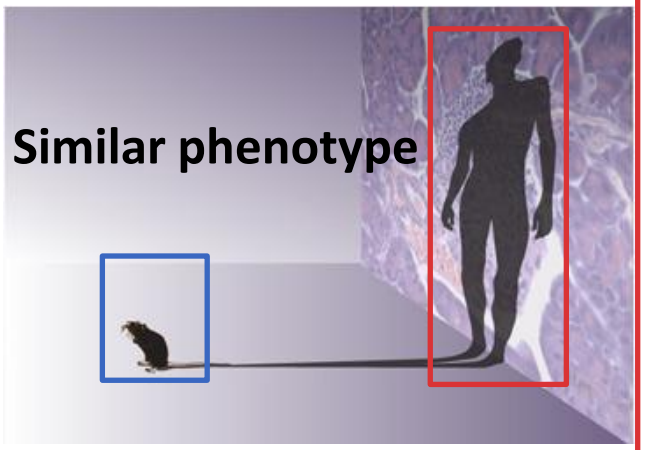
- **Ultrastructure disorganization**
- **Absence of I band**
- **Smaller sarcomere**
- **Contracted behavior**
- **Changes in the shape of mitochondria**
- **Increase in myosin diameter**

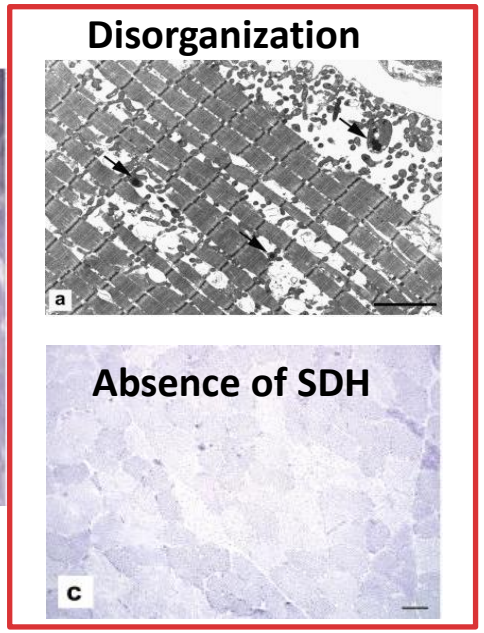
Deletion of TIEG Results in Altered Mitochondrial Activity



Fundamental Research → Clinical Research







Ronald G. et al. J of Clinical Investigation. 1991

Gittan K. et al. Neuromuscular Disorders. 2011

What is the mechanism of TIEG ?

Scope → new concepts of understanding metabolic disorders

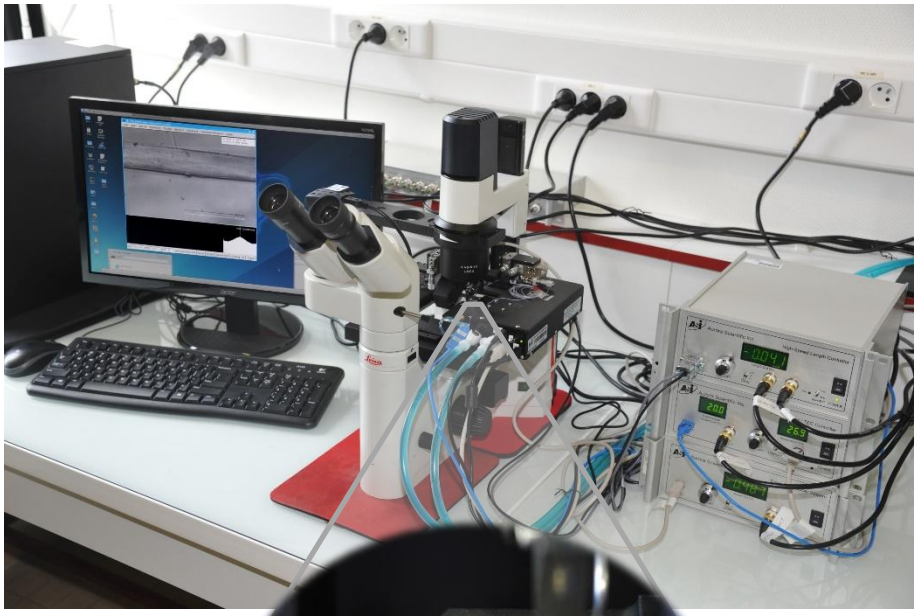
Can we identify mitochondrial pathologies ?

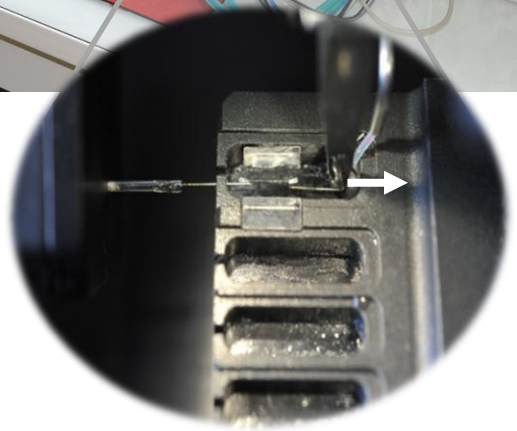
Scope → new means of diagnosis for energy metabolism disorders

Role of TIEG in Skeletal Muscle

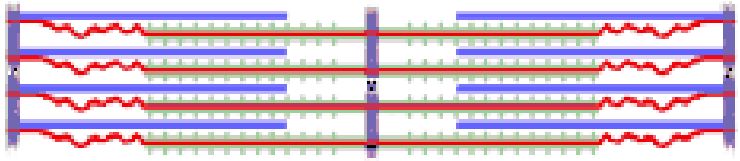
Morphological analysis

Functional analysis

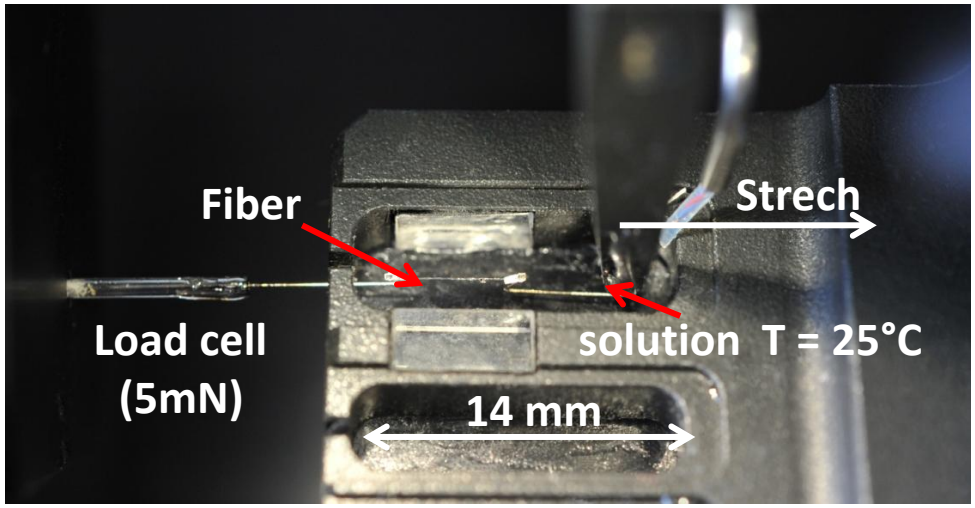


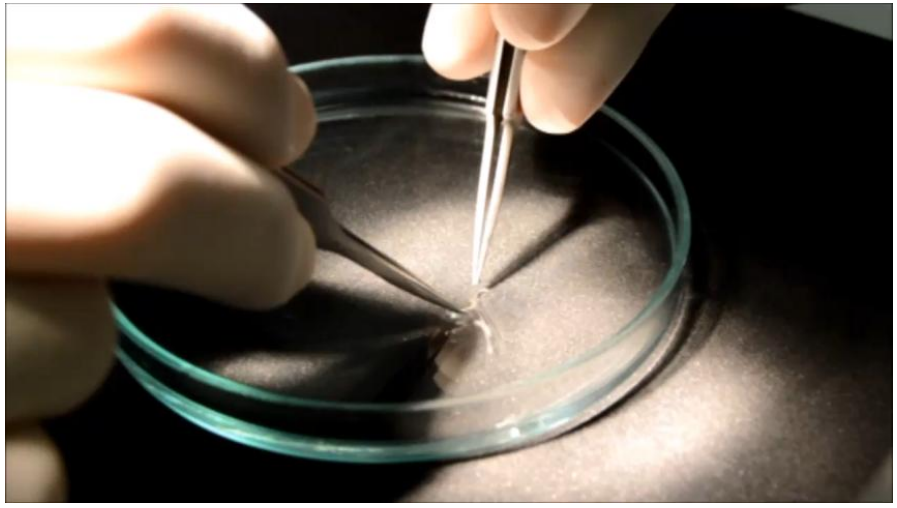


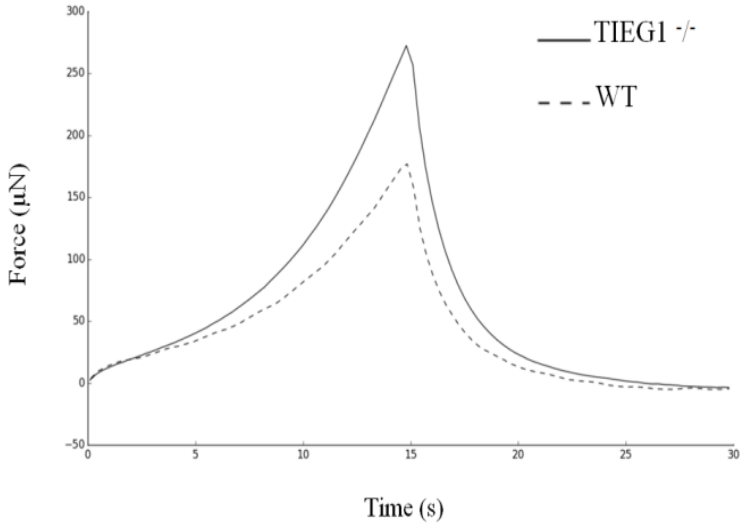
Muscle fiber



Platform for Multi-scale Characterization of Muscle Tissue







Published in final edited form as:
Muscle Nerve. 2017 March ; 55(3): 410–416. doi:10.1002/mus.25252.

Impact of TIEG1 on the structural properties of fast and slow twitch skeletal muscle

Malek Kammoun, PhD[1], Sandra Même, PhD[2], William Même, PhD[2], Malayannan Subramaniam, PhD[3], John R. Hawse, PhD[3], Francis Canon, PhD[1], and Sabine F. Bensamoun, PhD[1]

RESEARCH ARTICLE

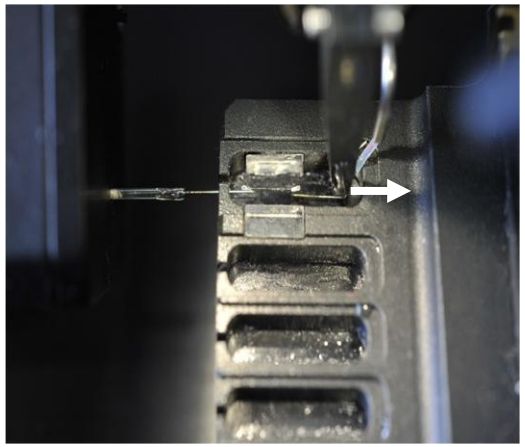
Impact of *TIEG1* Deletion on the Passive Mechanical Properties of Fast and Slow Twitch Skeletal Muscles in Female Mice

Malek Kammoun[1], Philippe Pouletaut[1], Francis Canon[1], Malayannan Subramaniam[2], John R. Hawse[2], Muriel Vayssade[1], Sabine F. Bensamoun[1]*

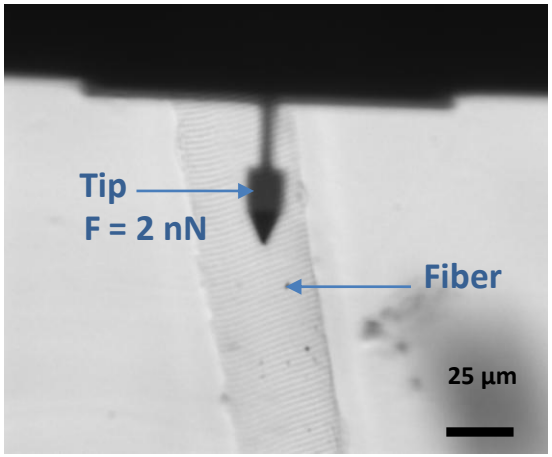
Platform for Multi-scale Characterization of Muscle Tissue

Two complementary mechanical tests

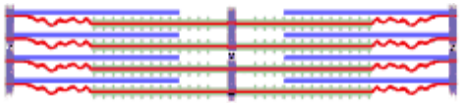
Longitudinal test



Transversal test (AFM)



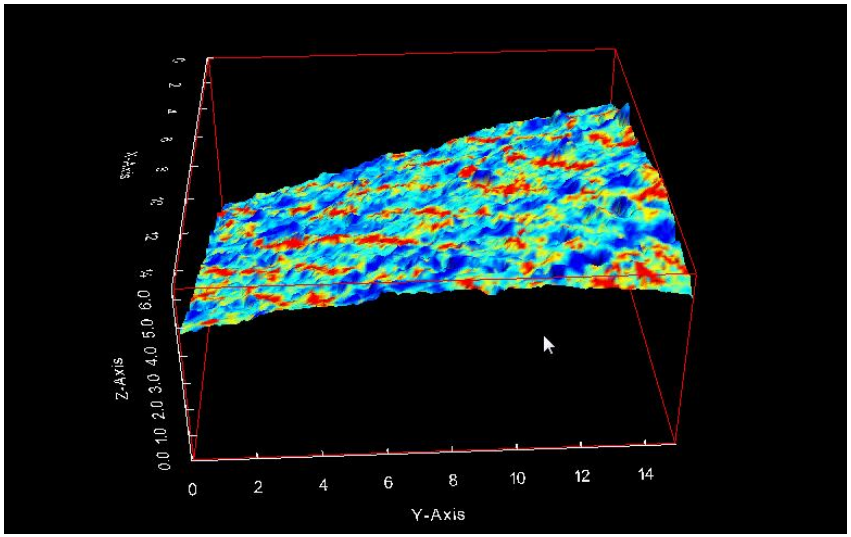
Functional behaviour of the fiber



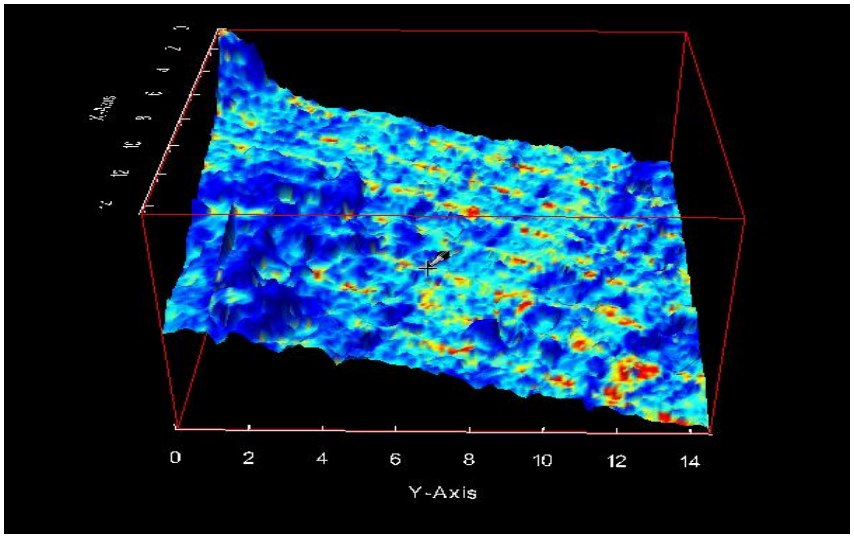
Organisation of the fiber structure

Transversal Mechanical Properties of TIEG KO Fibers

WT fiber



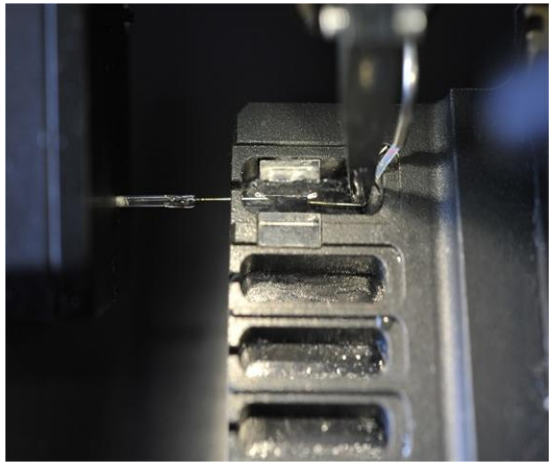
TIEG KO fiber



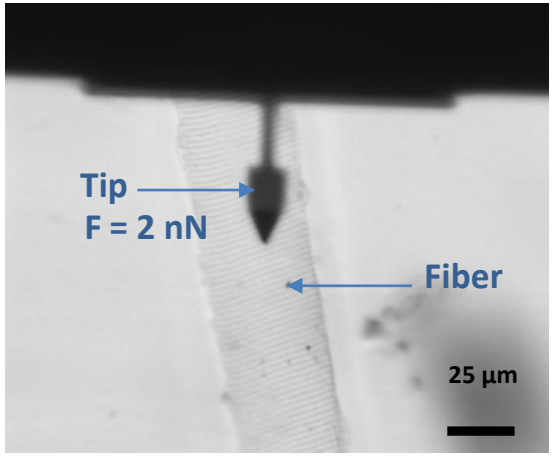
AFM technique indicated a less organized structure (lower resistance under the tip) which is revealed by a less rigid muscle composition for KO TIEG muscle fibers compare to WT muscle fibers

Perspectives: Development of a Multi-scale Muscle Platform

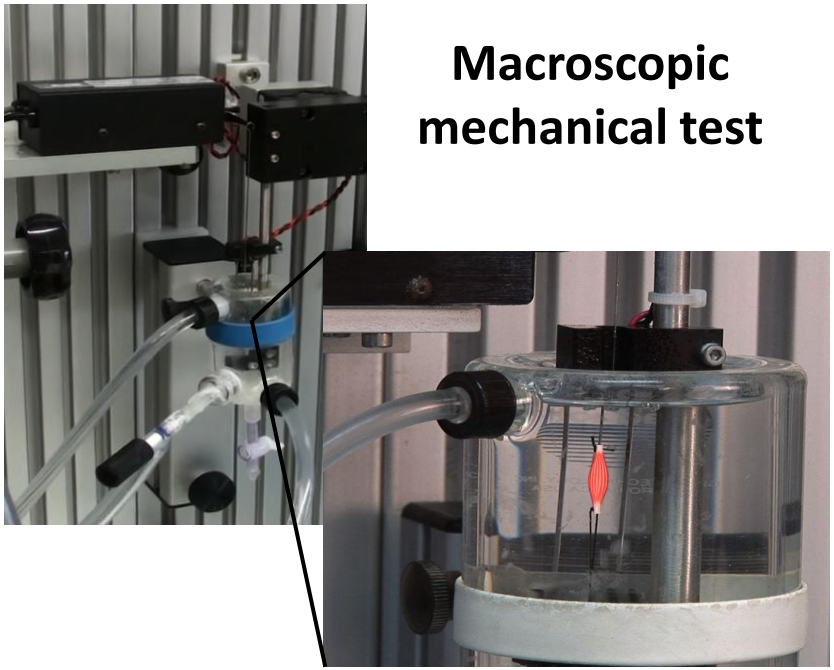
Microscopic mechanical test



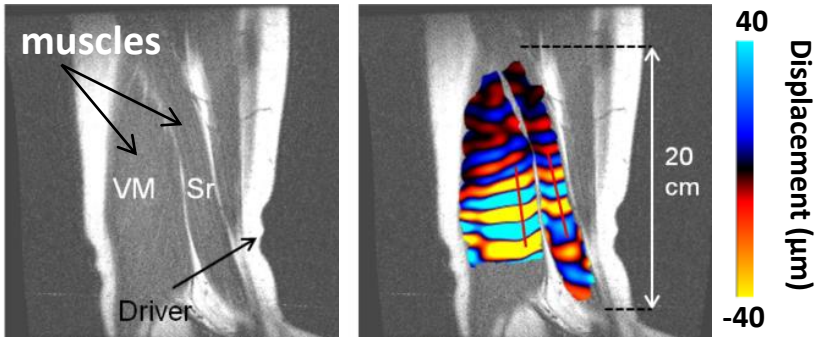
Microscopic test (AFM)



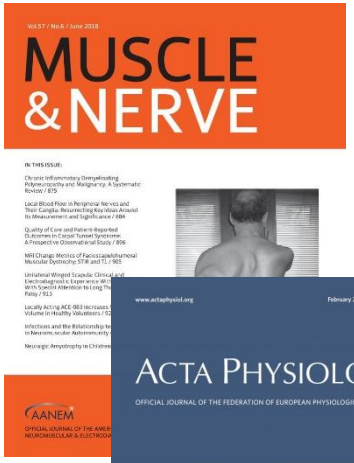
Macroscopic mechanical test

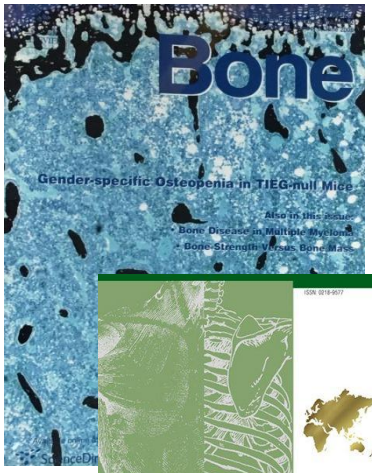


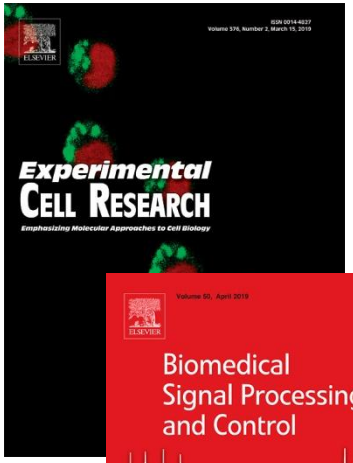
Macroscopic MRI elastography test

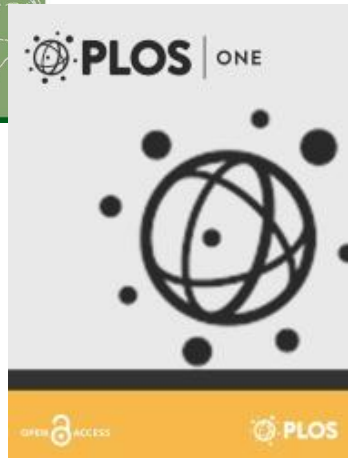


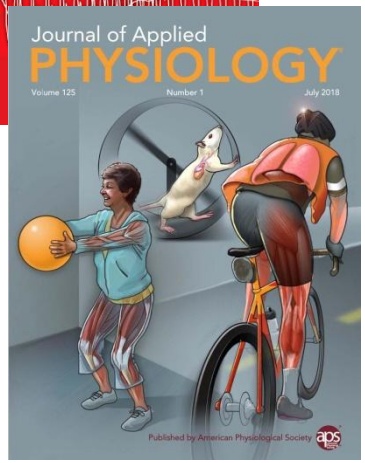
Valorization





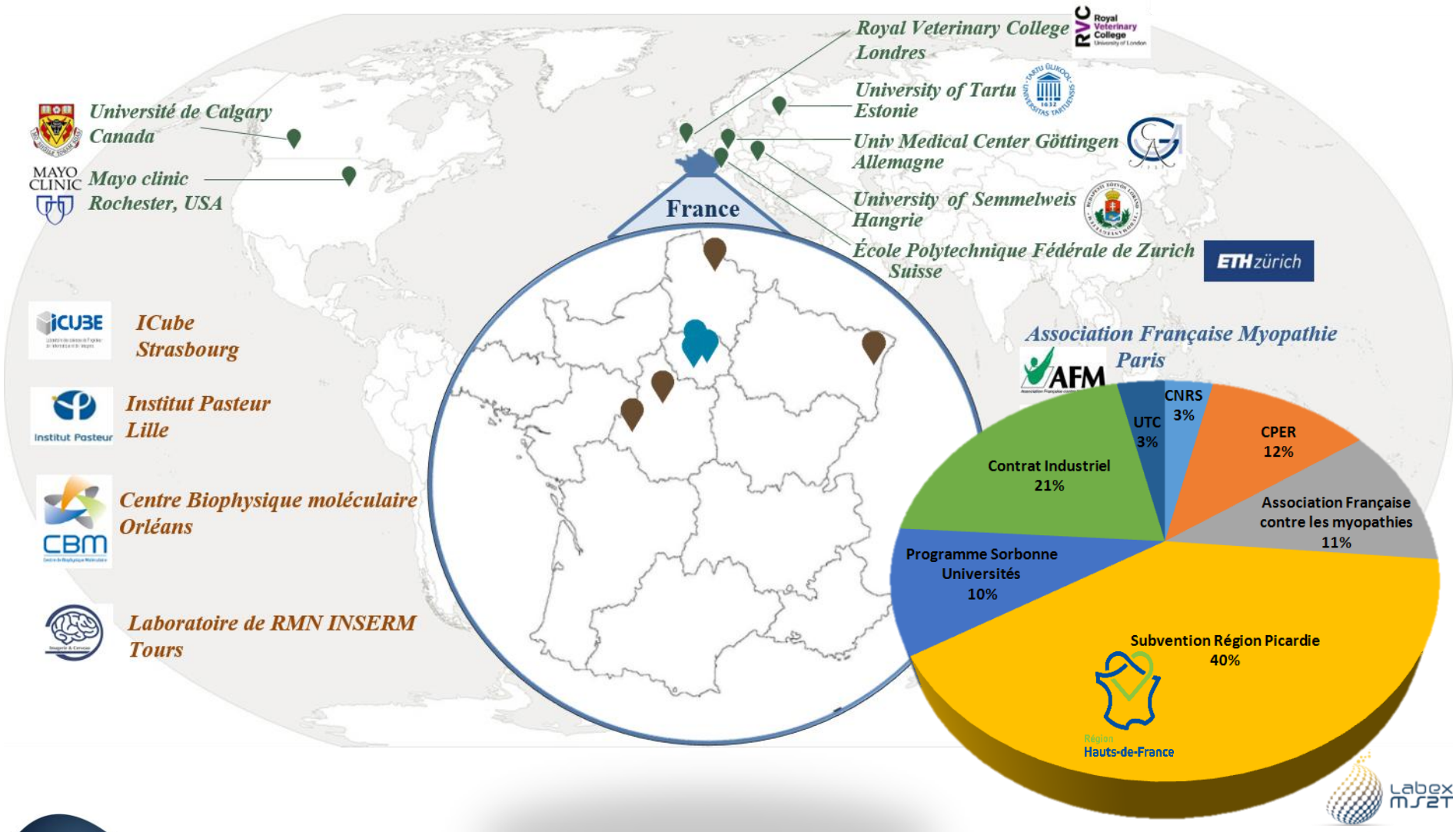






11 Articles

National and International network



2019: Bulding an International Research Network (ex GDRI)