THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

We honor the strength of our patients and families whose generosity fuels the search for cures!

George Adrian Calin, MD, Ph

Cancer Biology, Translational Molecular Pathology and Leukemia Depts.

MD Anderson Cancer Center, Houston, TX

Co-Director of the MD/PhD Program at UT Houston/ MDACC

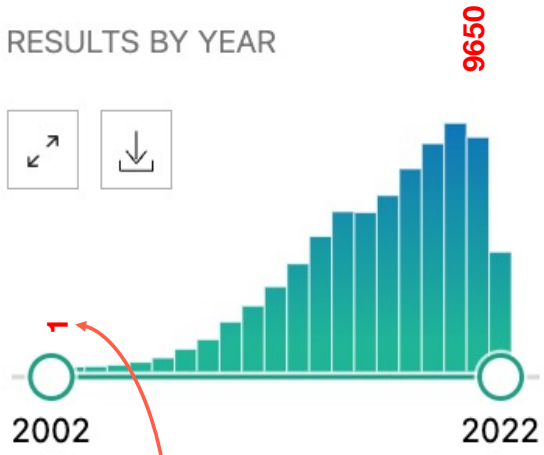
Really?!
Who are you little thing?
The son of a new genetics?

messengerRNA

We are very small
and non-coding!
But we can do
a big job
in your cells!
Size doesn't
matter!

microRNA

microRNAs & cancer in PubMed

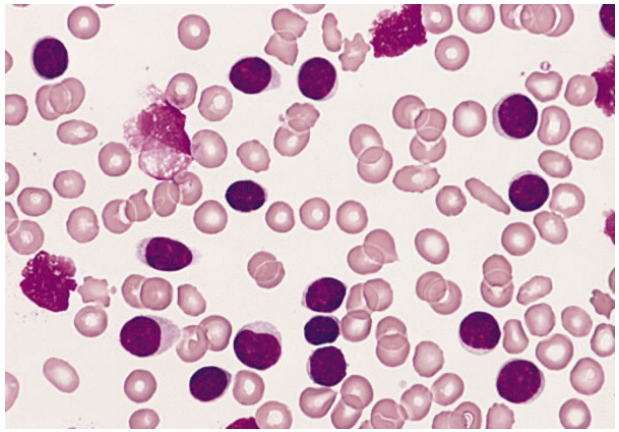


Frequent deletions and down-regulation of micro-RNA genes *miR15* and *miR16* at 13q14 in chronic lymphocytic leukemia

George Adrian Calin*, Calin Dan Dumitru*, Masayoshi Shimizu*, Roberta Bichi*, Simona Zupo†, Evan Noch*, Hansjuerg Aldler*, Sashi Rattan*, Michael Keating‡, Kanti Rai§, Laura Rassenti¶, Thomas Kipps¶, Massimo Negrini*, Florencia Bullrich*, and Carlo M. Croce*‖

CLL – the “bipolar” leukemia

90-95%
Indolent to aggressive CLL in years



Low miR-15/16 levels

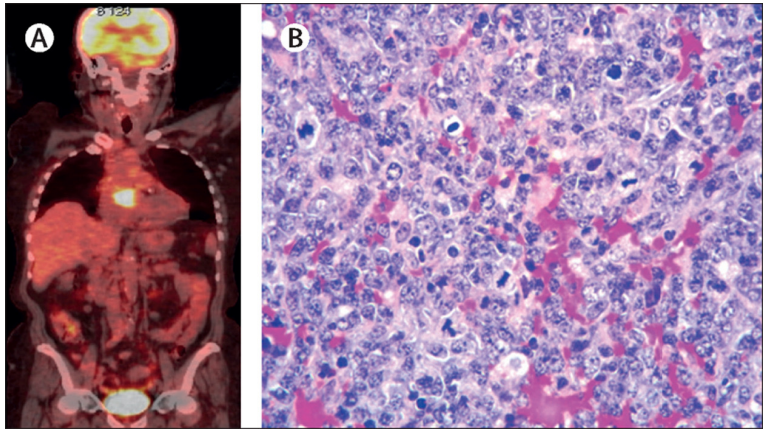
▼

high BCL2 Protein expression

▼

great clinical activity of Venetoclax

5-10%
Richter’s transformation

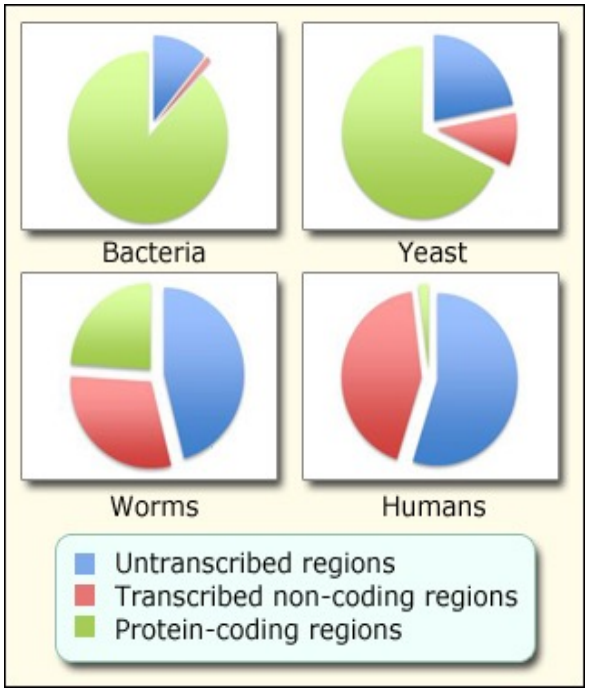


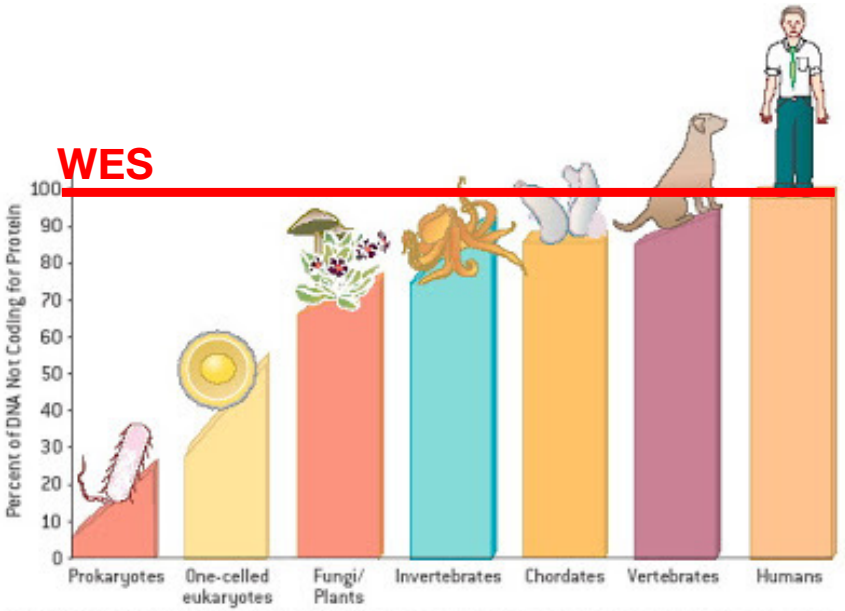
(Marra A et al, "Richter's transformation in the heart" Lancet Oncology 2021)

“Unknown” mechanism

(low P16 without deletion,
mutations in TP53 in some patients)

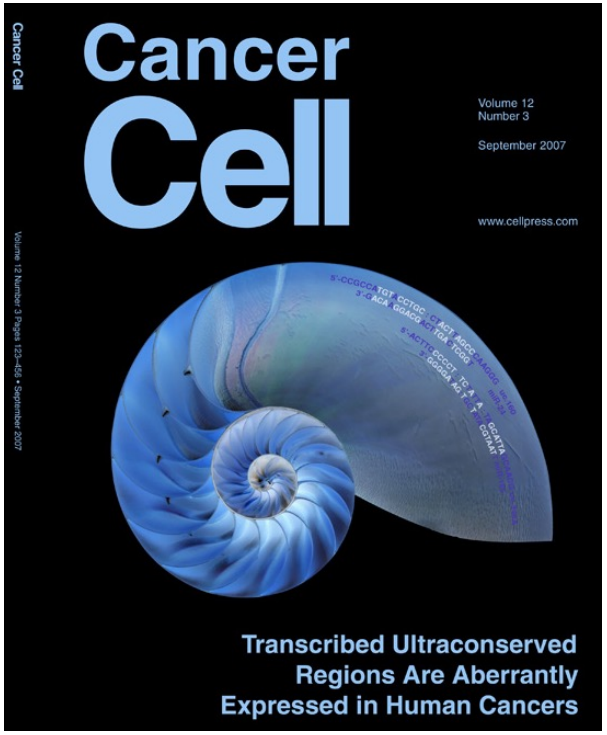
The non-codingDNA paradox:
we are what our non-codingDNA is !





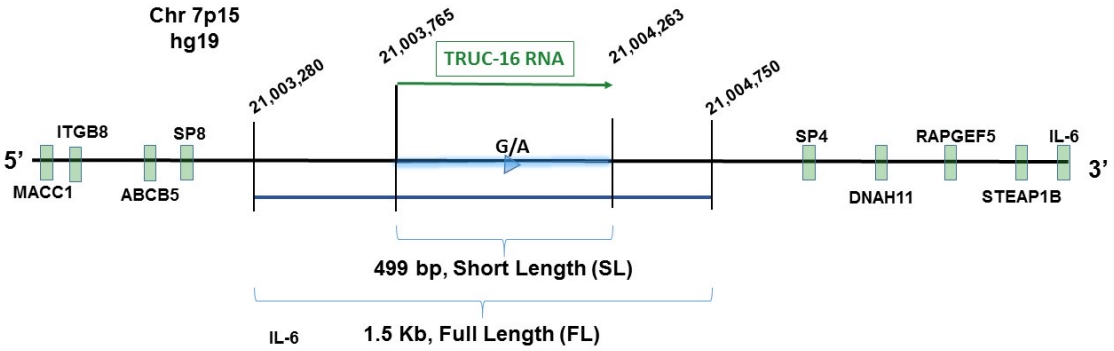
NONPROTEIN-CODING SEQUENCES make up only a small fraction of the DNA of prokaryotes. Among eukaryotes, as their complexity increases, generally so, too, does the proportion of their DNA that does not code for protein. The noncoding sequences have been considered junk, but perhaps it actually helps to explain organisms' complexity.

Genomic ultraconservation: paradigms

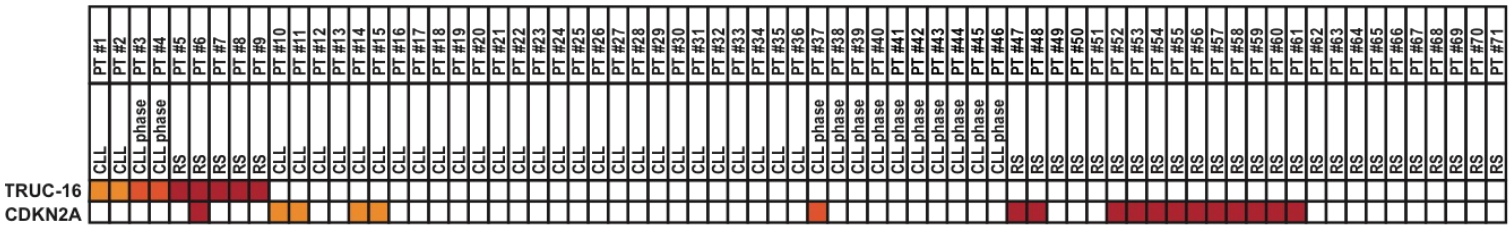


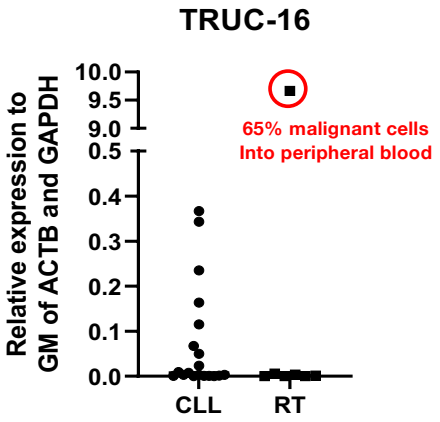
- **~ 5% of the human genome is more conserved than would be expected based on neutral evolution since the split with rodents 300 millions years ago;**
- **They exhibit almost no natural variation within the human population;**
- **The probability of finding one such element in 2.9 billion bases is less than 10^{-22} under a neutral evolution model.**

A transcribed Ultraconserved non-coding element regulates P16 expression



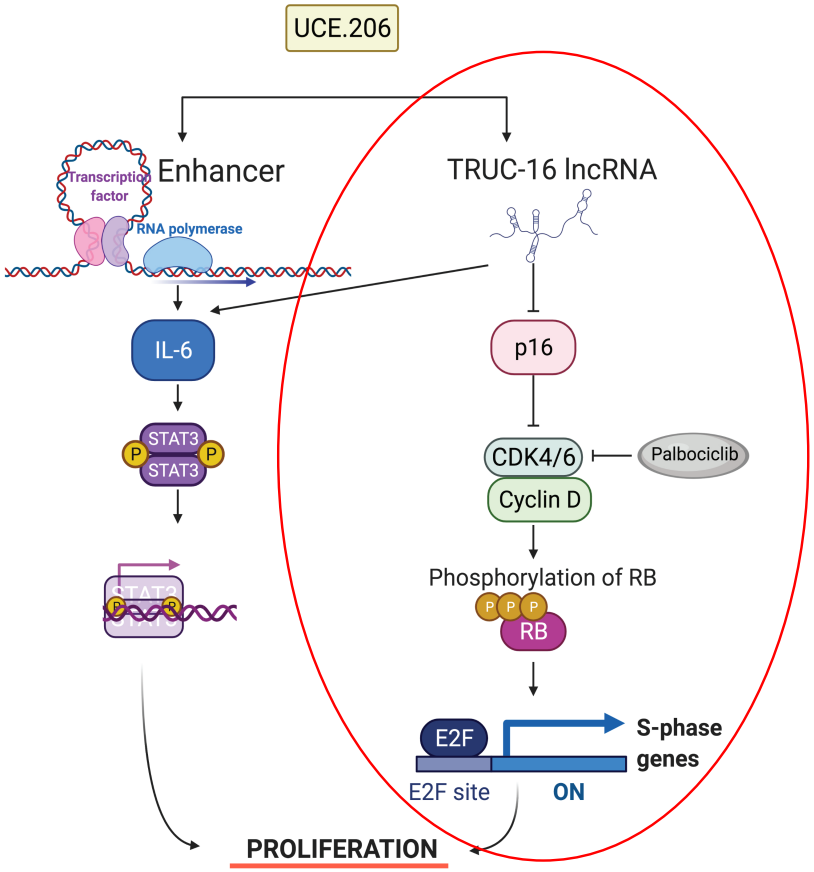
Linda Fabris

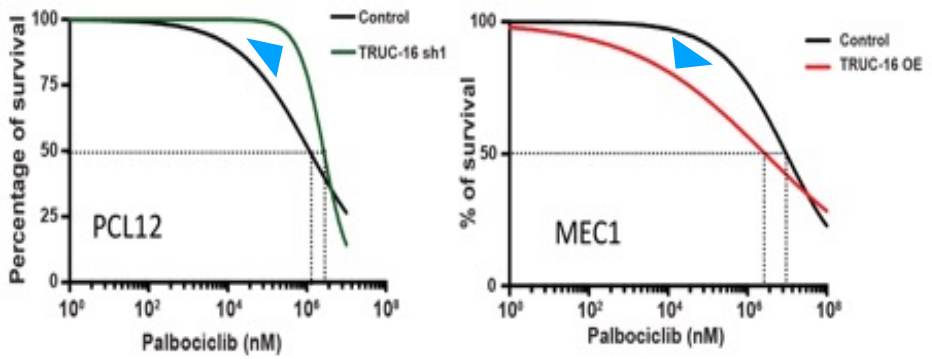




(Fabris et al, in revision Nature Communication 2025)

From ultraconservation to repurposing drugs: CDK4/6 inhibitors in RT?





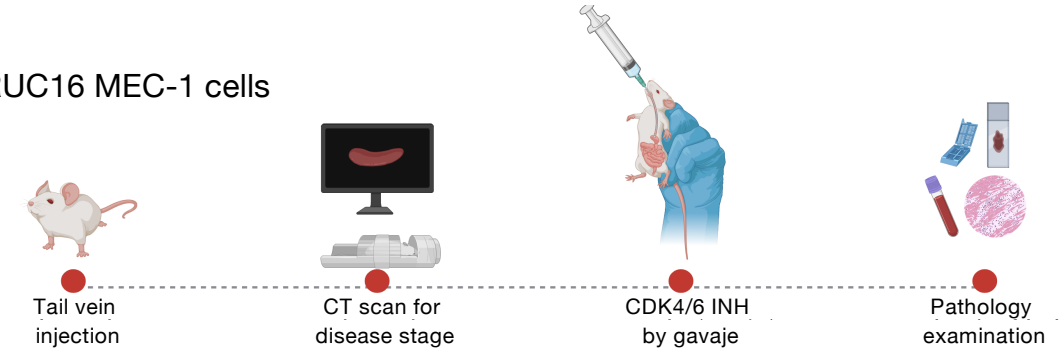
(Fabris et al, in revision Nature Communication 2025)

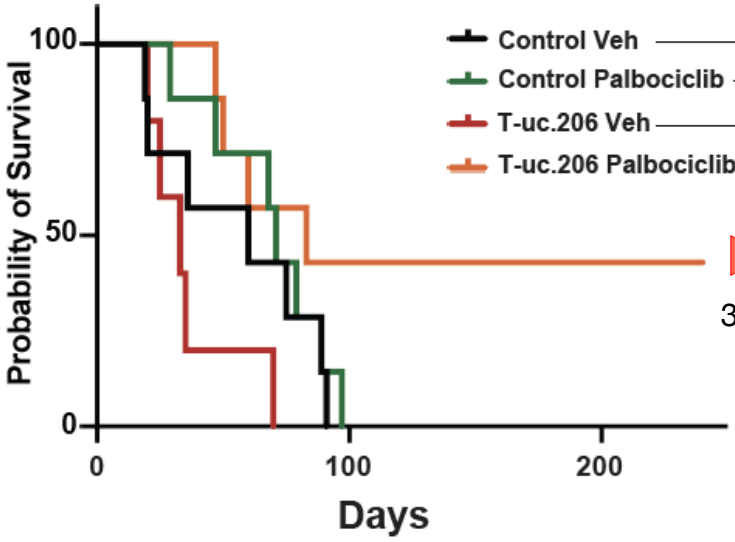
Yes, CDK4/6 inhibitors in RT !

Linda Fabris

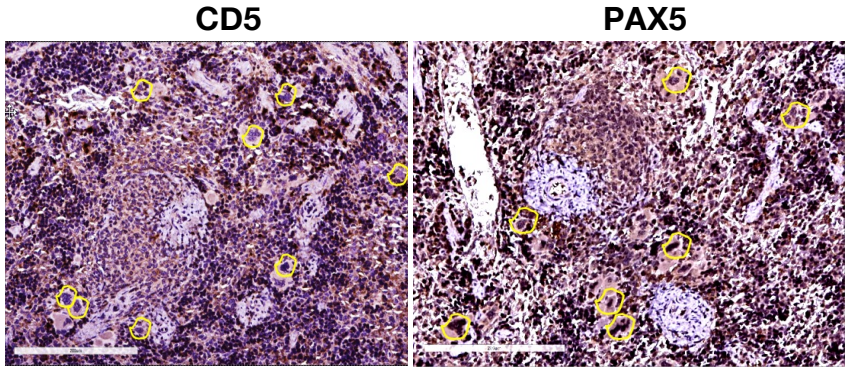
Sam Akanksha

High TRUC16 MEC-1 cells





3 out of 8 mice

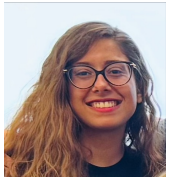


(Fabris et al, in revision Nature Communication 2025)

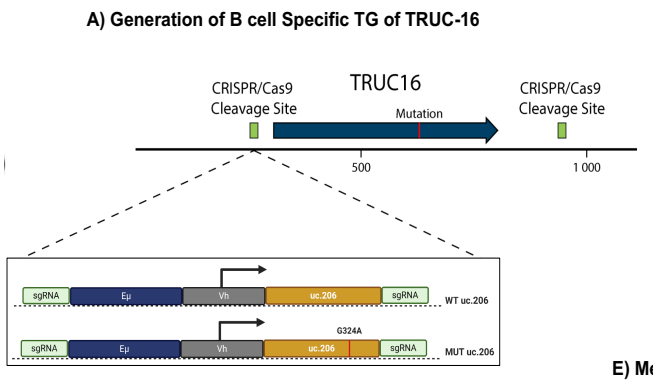
TRUC-16 B-cell specific TG mouse model

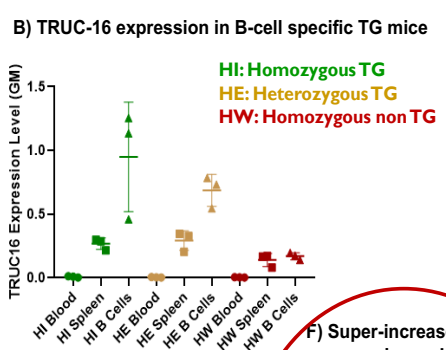
(Erik Knutsen and Kinga Nemeth and Zara de Leon;
Collaboration with Mihai Gagea and Sabrina Bertilaccio)

Kinga Nemeth



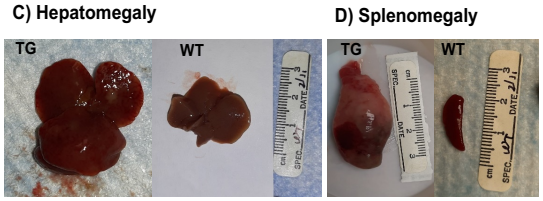
Zara de Leon

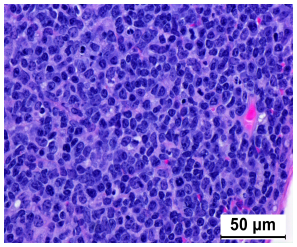


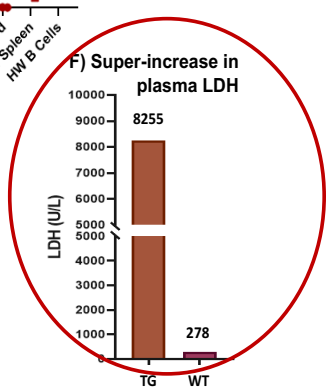


Erik Knutsen

Swati Mohapatra





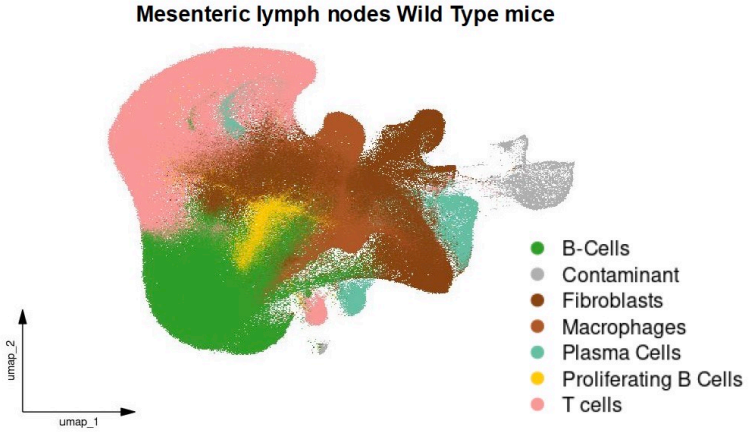


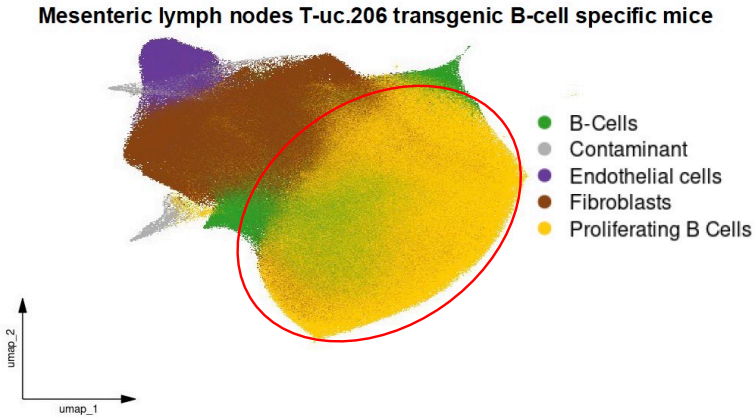
TRUC-16 transgenic mice develop a disease similar to Richter's transformation. (A) TRUC16 is under the control of V_H promoter and IgH-Eμ enhancer that specifically induces expression of the transgene in the B cells (B) The confirmation of TRUC-16 high expression in tissues enriched in B cells; (C to F) Specific characteristics of the RT reproduced in TRUC-16 TG.

(Nemeth et al, in preparation 2025)

B-cell proliferation in uc-206 TG mice with RT

(Spatial transcriptomics in collaboration with Humam Kadara)





(Nemeth et al, in preparation 2025)

A phase 1 trial of ibrutinib plus palbociclib in previously treated mantle cell lymphoma

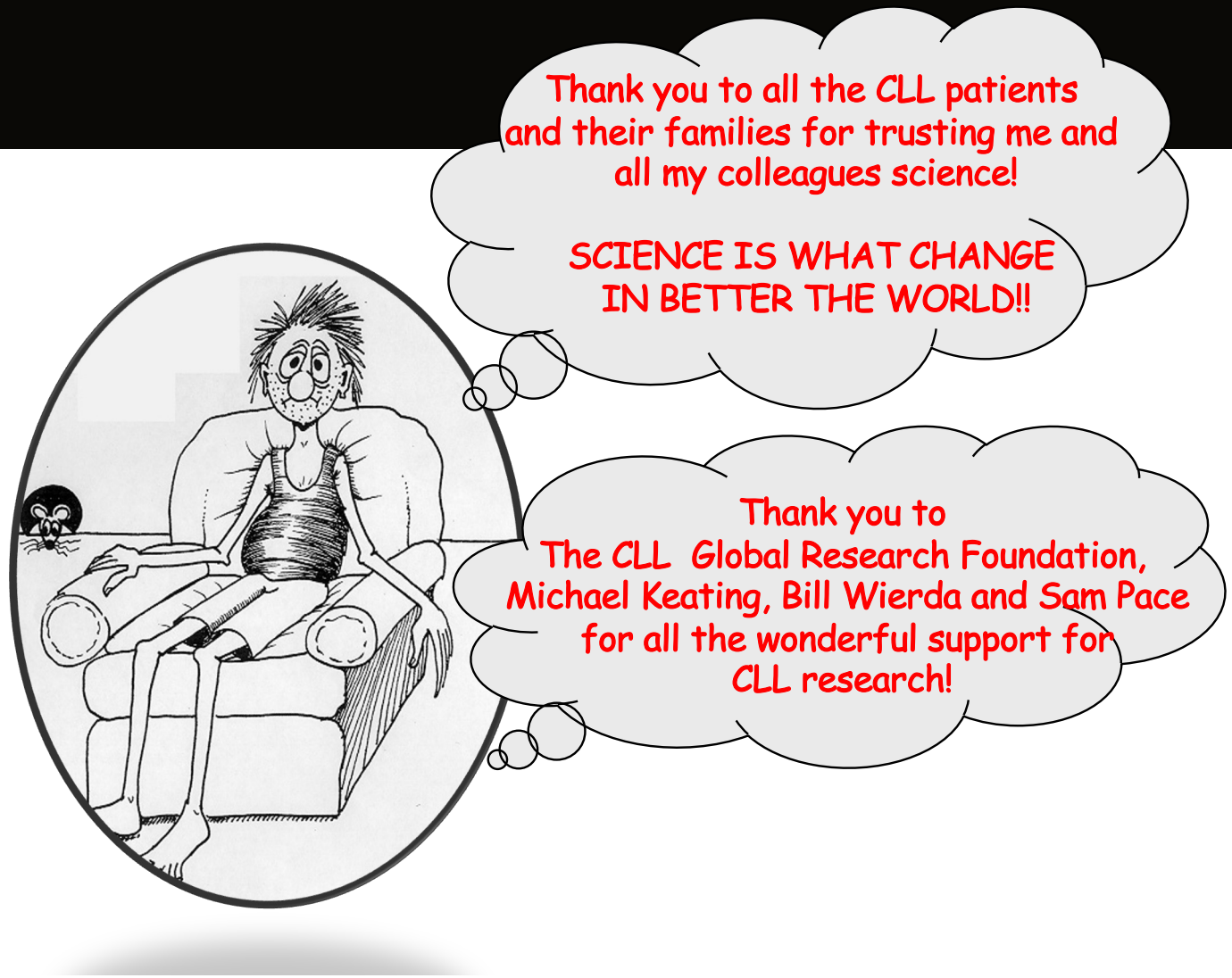
Peter Martin,[1,2] Nancy L. Bartlett,[3] Kristie A. Blum,[4] Steven Park,[5] Kami Maddocks,[4] Jia Ruan,[1,2] LeAnn Ridling,[3] Christopher Dittus,[5] Zhengming Chen,[6] Xiangao Huang,[1,7] Giorgio Inghirami,[1,7] Maurizio DiLiberto,[1,7] Selina Chen-Kiang,[1,7] and John P. Leonard[1,2]

[1]Meyer Cancer Center, Weill Cornell Medicine, New York, NY; [2]Department of Medicine, New York Presbyterian Hospital, New York, NY; [3]Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO; [4]The Ohio State University Comprehensive Cancer Center, Columbus, OH; [5]Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC; and [6]Department of Healthcare Policy and Research and [7]Department of Pathology, Weill Cornell Medicine, New York, NY

KEY POINTS

- **Ibrutinib 560 mg daily plus palbociclib 100 mg on days 1 to 21 of each 28-day cycle could be safely administered to patients with previously treated MCL.**
- **Complete responses and duration of response (median, >2 years) were high relative to studies of single-agent ibrutinib.**

Single-agent ibrutinib is active in patients with previously treated mantle cell lymphoma (MCL); however, nearly half of all patients experience treatment failure during the first year. We previously demonstrated that prolonged early G1 cell cycle arrest induced by the oral, specific CDK4/6 inhibitor palbociclib can overcome ibrutinib resistance in primary human MCL cells and MCL cell lines expressing wild-type Bruton's tyrosine kinase (BTK). Therefore, we conducted a phase 1 trial to evaluate the dosing, safety, and preliminary activity of palbociclib plus ibrutinib in patients with previously treated mantle cell lymphoma. From August 2014 to June 2016, a total of 27 patients (21 men, 6 women) were enrolled. The maximum tolerated doses were ibrutinib 560 mg daily plus palbociclib 100 mg on days 1 to 21 of each 28-day cycle. The dose-limiting toxicity was grade 3 rash. The most common grade 3 to 4 toxicities included neutropenia (41%), thrombocytopenia (30%), hypertension (15%), febrile neutropenia (15%), and lung infection (11%). The overall and complete response rates were 67% and 37%, and with a median follow-up of 25.6 months, the 2-year progression-free survival was 59.4% and the 2-year response duration was 69.8%. A phase 2 multicenter clinical trial to further characterize efficacy is now ongoing. The current trial was registered at www.clinicaltrials.gov as #NCT02159755. (*Blood*. 2019;133(11):1201-1204)


Thank you to all the CLL patients and their families for trusting me and all my colleagues science!
SCIENCE IS WHAT CHANGE IN BETTER THE WORLD!!
Thank you to
The CLL Global Research Foundation, Michael Keating, Bill Wierda and Sam Pace for all the wonderful support for CLL research!