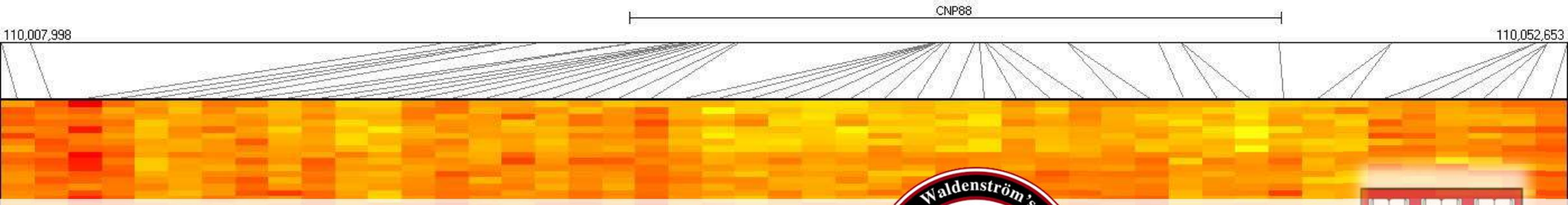
WM Genomics

Zachary Hunter, PhD

Making Sense of the Science of WM

Zachary Hunter
Bing Center for WM
Dana-Farber Cancer Institute
Harvard Medical School



Dana-Farber Cancer Institute

Bing Center for WM
Research at the
Dana-Farber
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Harvard
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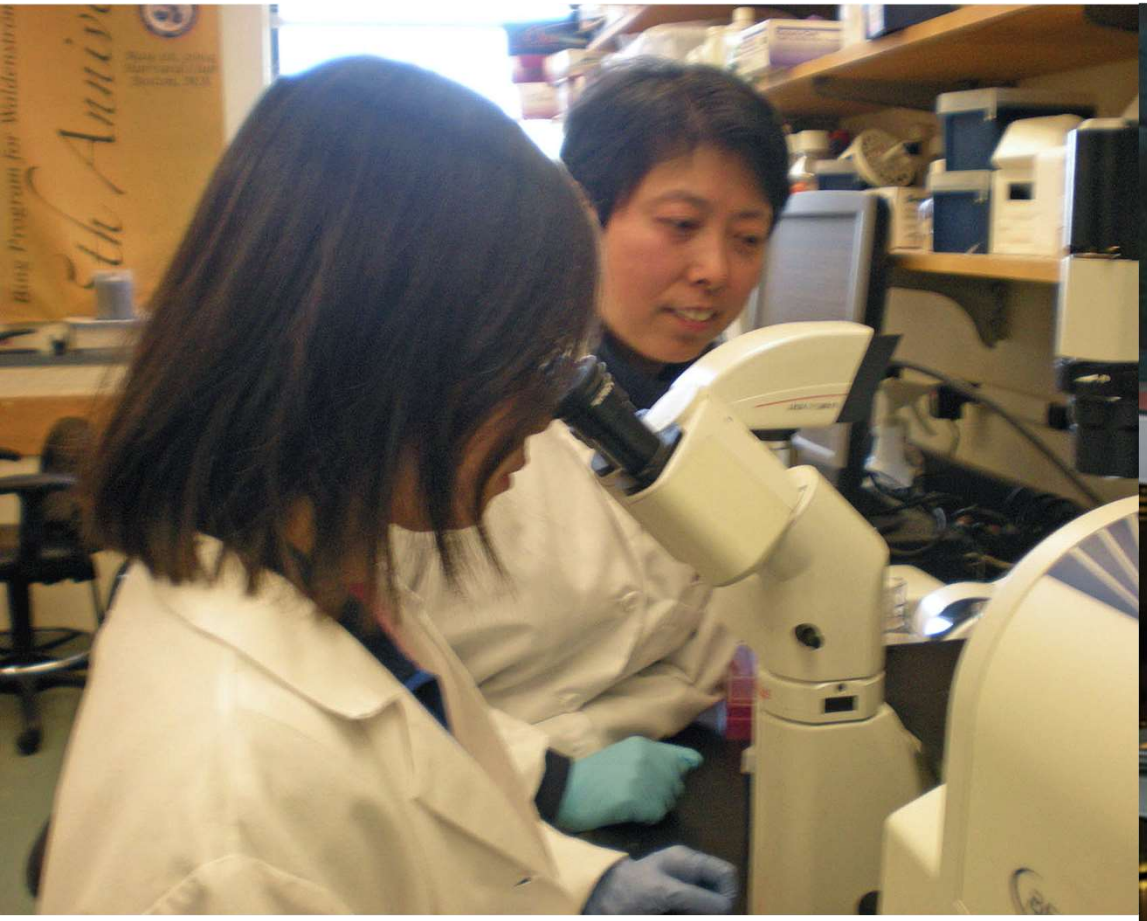
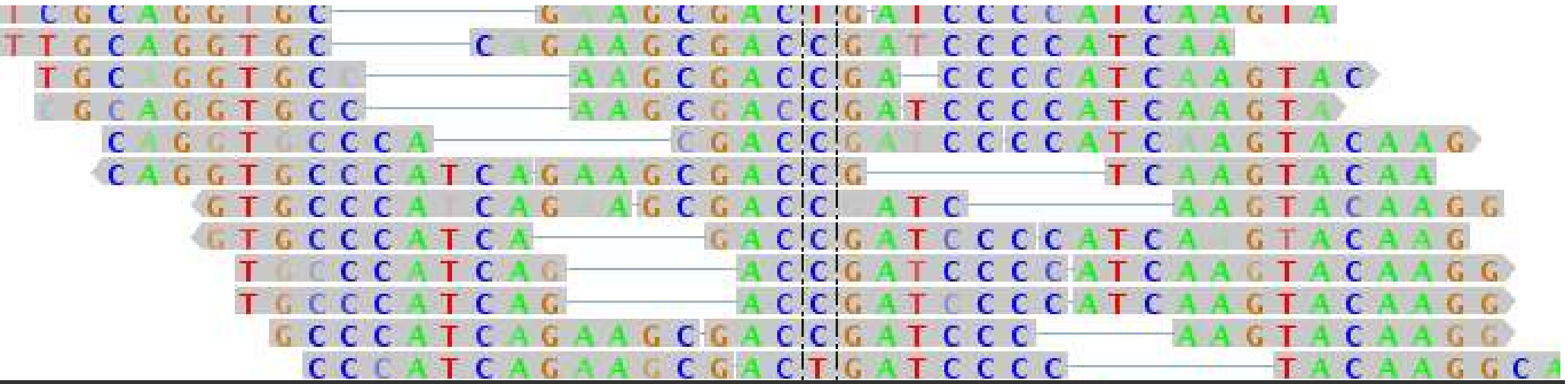
School



Dana-Farber
Cancer Institute

Bing Center for WM Research at the Dana-Farber Cancer Institute

Bing Center for Waldenström's Macroglobulinemia



Understanding Genetics

If you only had four letters to work with, what kind of story could you tell?

Genomics is easy…

DNA

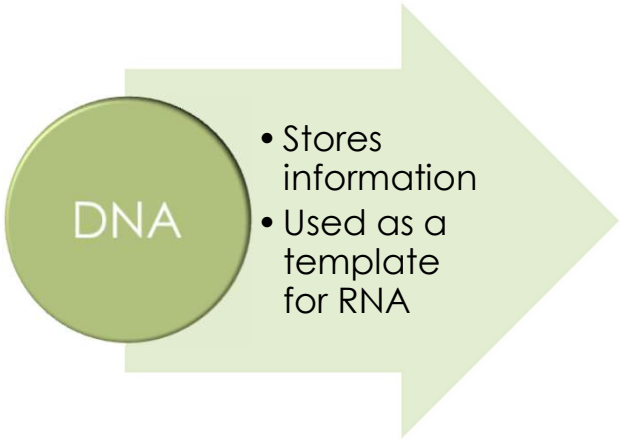
RNA

- Deoxyribonucleic Acid (DNA) is made of complex molecules called nucleotides. There are 4 types abbreviated A,T,C,G.
- Nucleotide bases form stables pairs: A-T and C-G. Two complimentary strands of these bases form DNA.
- DNA is broken into 23 long strands known as chromosomes.
- The sections of the DNA that contain instructions on how to build proteins are called genes.
- Genes in the DNA are transcribed into a single strand of similar nucleotides called Ribonucleic Acid (RNA) and this “message” is processed by the cell and turned into protein.

Something easy with ~ 3,000,000,000 pieces can be really complicated…

- For context, computers operate with just two "bases" 0 and 1.
- With enough 0s and 1s it turns out you can make computer's do some pretty impressive and complicated stuff.
- DNA has 4 bases, x 3 Billion with a lot more chemical and spatial annotation.
- This makes IBM's Watson or ChatGPT look simple by comparison, even if they do beat us at Jeopardy

DNA – RNA – Protein



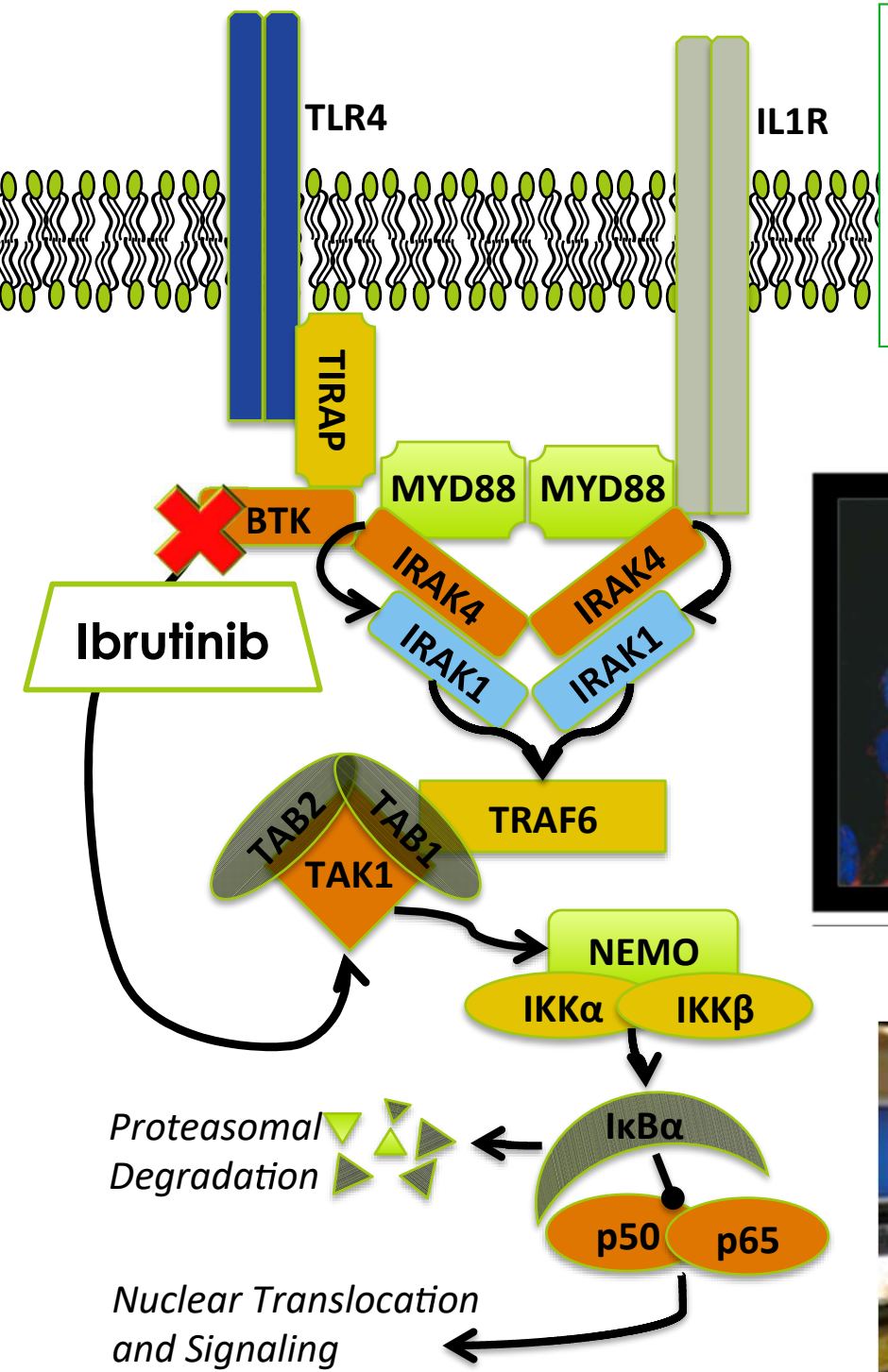
- ***Genes are regions of the DNA that are transcribed into RNA***
- ***RNA carries the DNA code out into the rest of the cell where it can be used as instructions to make protein***

Mutation and Cancer

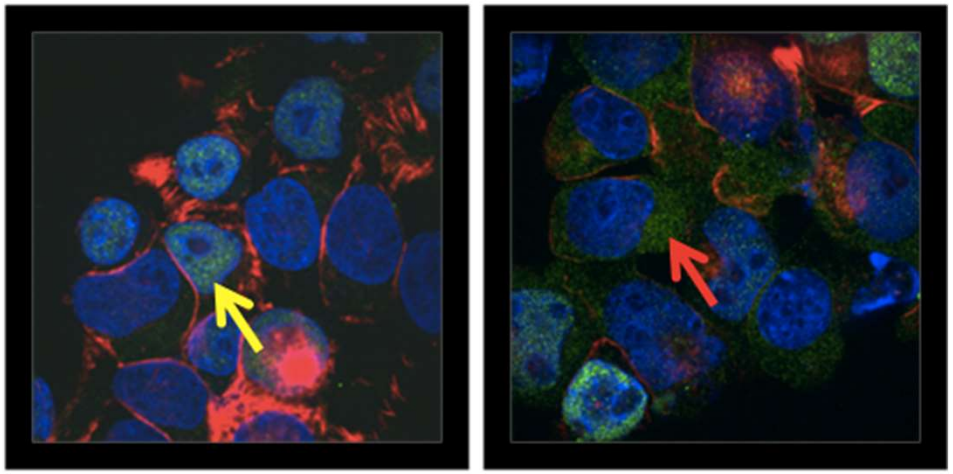
- Cancer can be caused by accidental changes in the genome known as mutations
- As these accumulate, genes start to gain new functions, or lose old ones
- At the point that the cells start to multiply in an uncontrolled way, we call it cancer

MYD88 Signaling

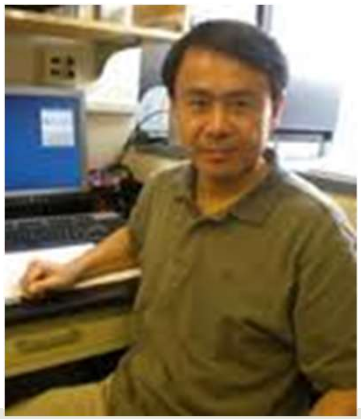
A single base pair mutation the gene MYD88 is found in over 90% of WM



NFKB Nuclear Translocation in The BCWM.1 Cell Line



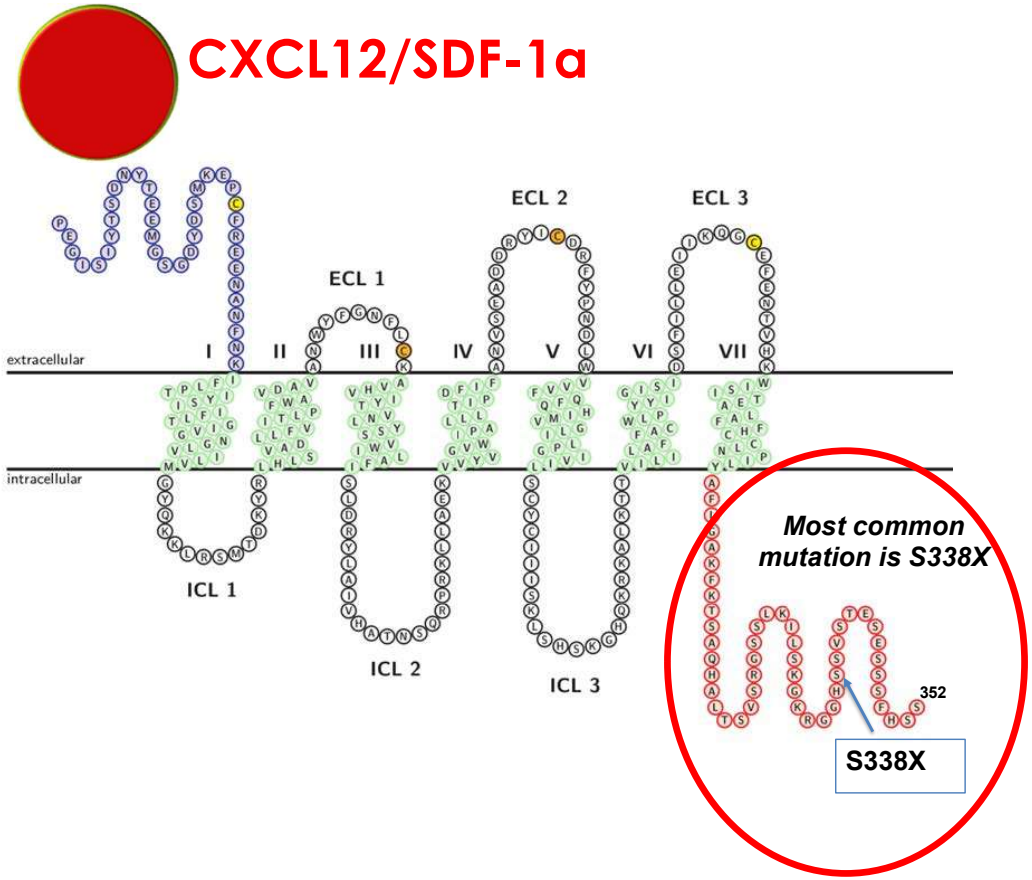
Control | MYD88 Inhibitor



Guang Yang, PhD
Yang et al. Blood 2013

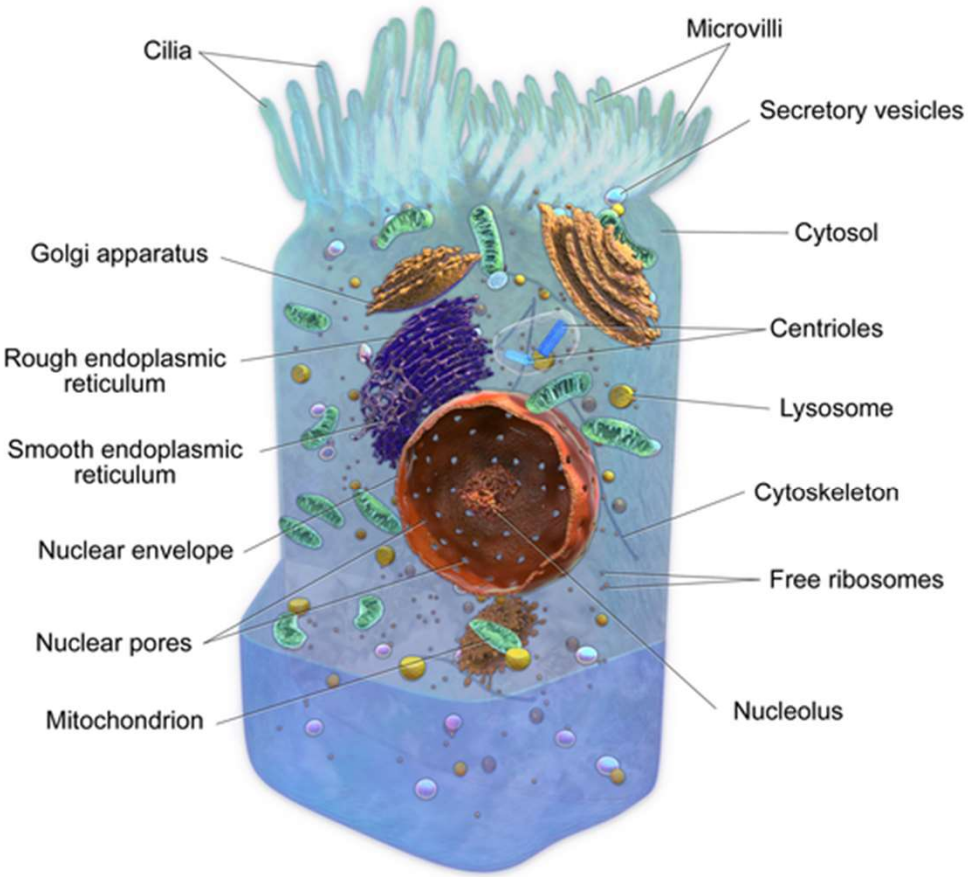
WHIM-like CXCR4 mutations in Waldenstrom's Macroglobulinemia

- 30-40% of WM patients
- Occur in the C-terminal domain (same site as WHIM patients)
- Nonsense and frameshift mutations
- Associated with high IGM, hyperviscosity.
- Multiple CXCR4 mutations can be present within an individual patient.



Hunter et al, Blood 2013; Rocarro et al, Blood 2014: Poulain et al, Blood 2016; Poulain et al, CCR 2016; Xu et al, BJH 2016; Varettoni et al, Haematologica 2017.

How to make it all fit…

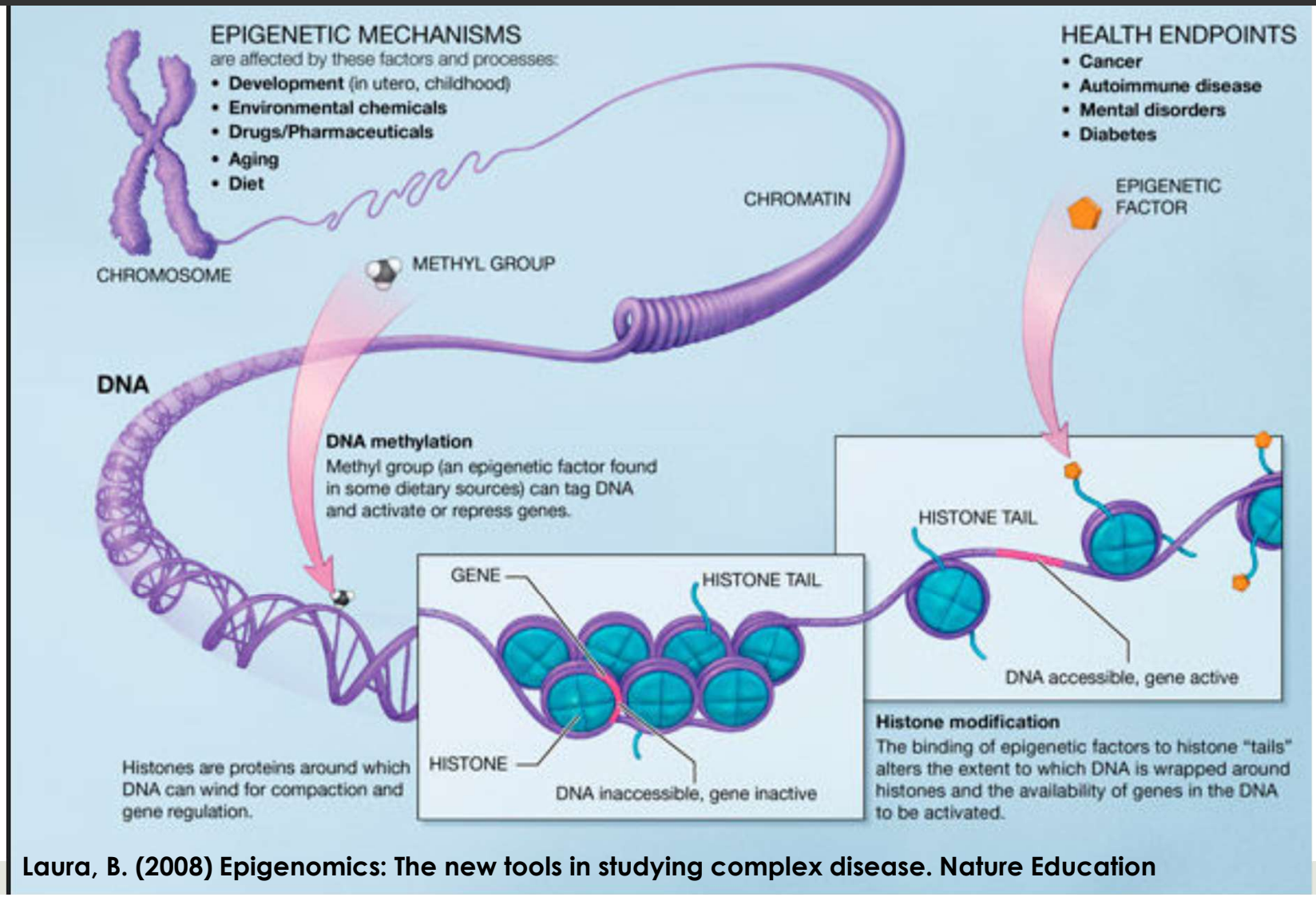


Anatomy of a Cell

- 3 billion base pairs strung end to end is about 40 inches in length.
- This quantity of DNA resides inside the nucleus of every cell in your body
- Needless to say, this is a tightly controlled process.

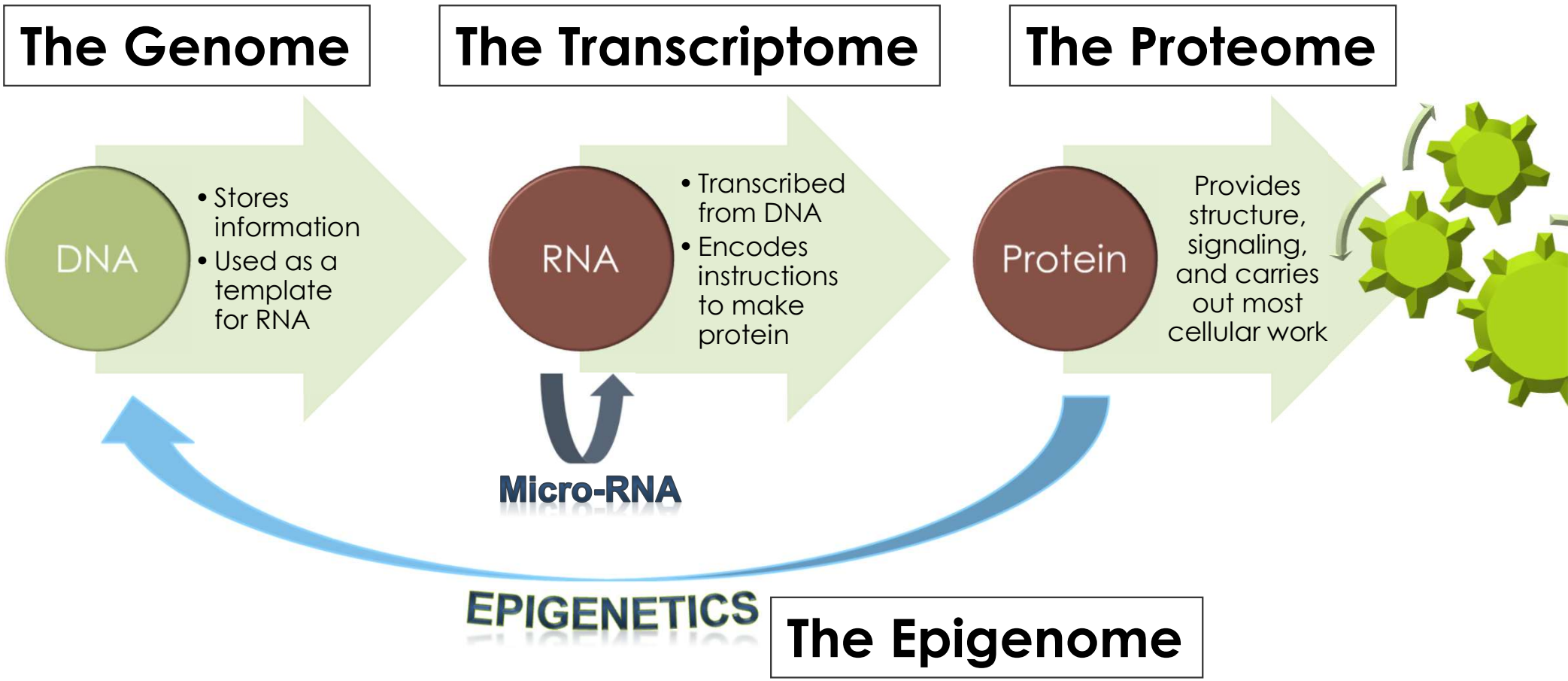
Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". *WikiJournal of Medicine* **1** (2

Our apologies, the DNA you are looking for is temporarily unavailable…



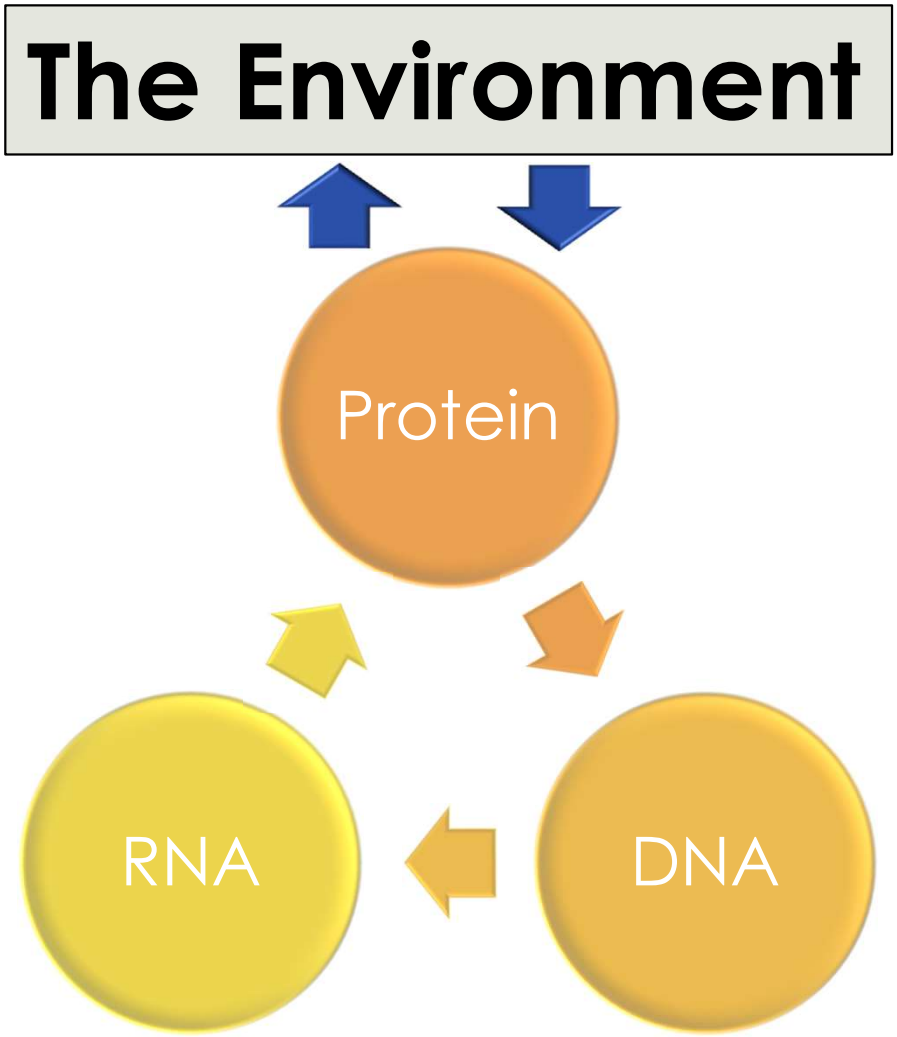
Laura, B. (2008) Epigenomics: The new tools in studying complex disease. Nature Education

Introducing the "omes"



The genome as the cell's operating system

The operating system of your computer (Windows/Max OSX/Linux) provides a set of tools to allow programs to be loaded and run. Every laptop may have the same operating system, but no one uses their laptop in exactly the same way



Identical Twin Studies

While identical twins share many things in common, they also have very different lives, unique personalities, get different diseases and after a number of years can look quite different from each other.

theguardian | TheObserver

Why do identical twins end up having such different lives?

Their genes are exactly the same, so why don't identical siblings' lives follow more similar patterns? The scientist behind a pioneering 21-year study believes he has the answer

Robin McKie
The Observer, Saturday 1 June 2013

Jump to comments (0)

Every Cell in Your Body has the Same DNA. Why Don't They Act Like It?

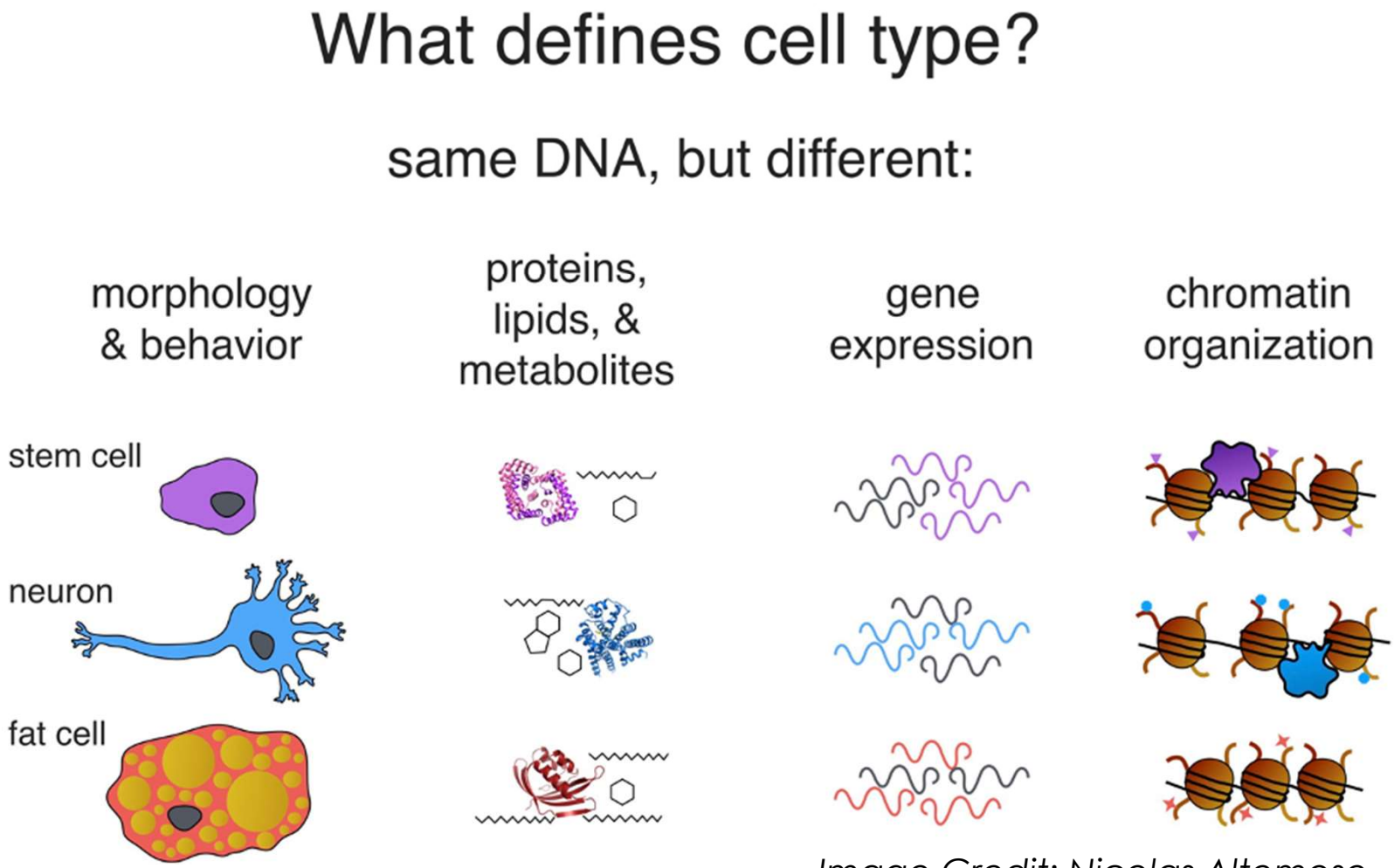
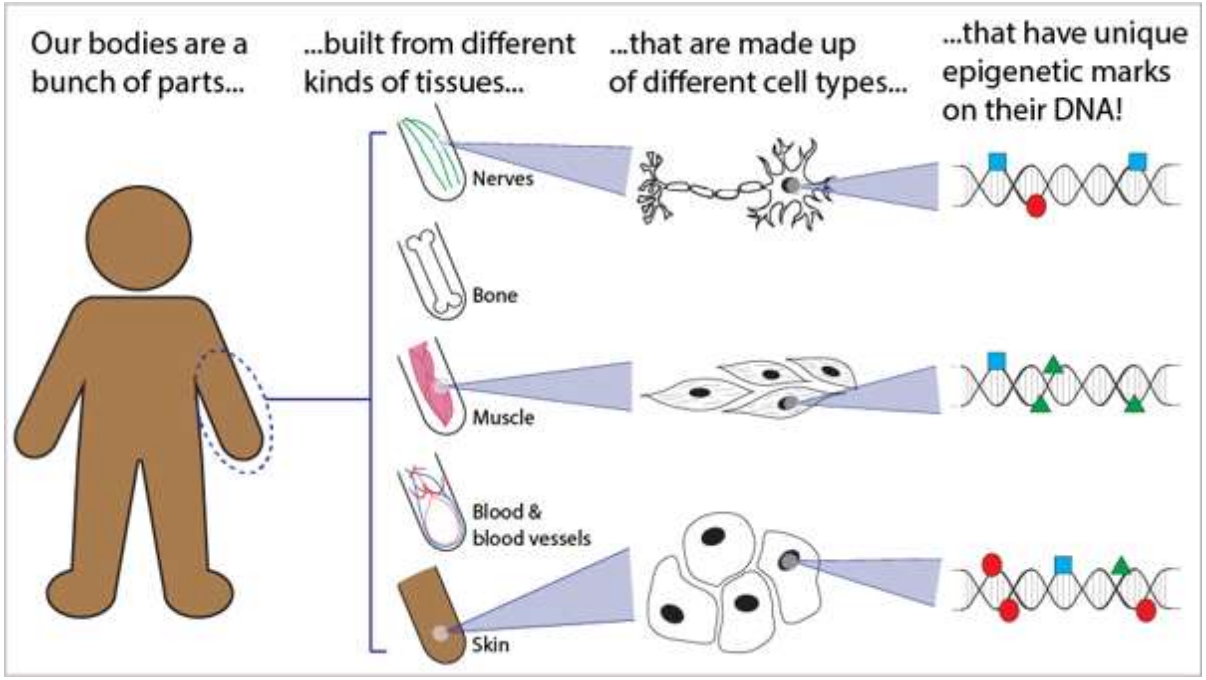


Image Credit: Nicolas Altemose.

Epigenetics and Cancer



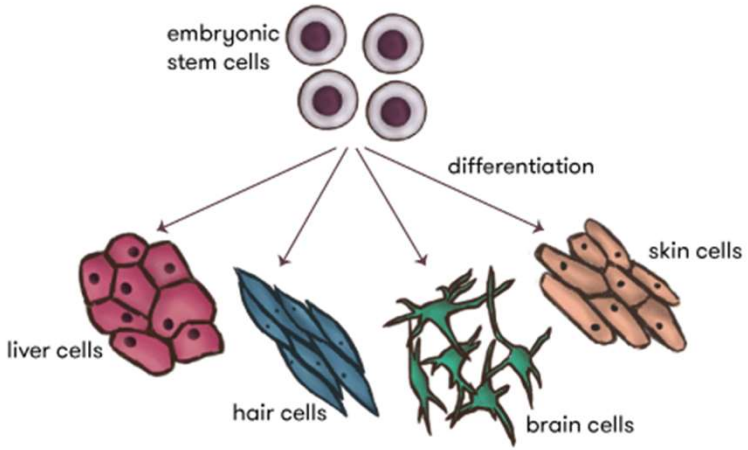
https://www.thetech.org/ask-a-geneticist/articles/2019/epigenetics-and-cell-types/

The epigenome controls which parts of the genome the cell can see so each cell type effectively has a unique genome.

Some epigenetic of these gene controls are dynamic and change with the environment and some are designed to be stable and define the cell type. In cancer, mutations in the DNA and mistakes in epigenomic maintenance can let cells access parts of the genome that they are not supposed to see and even start to lose some of their cell type identity.

Cell of Origin in Cancer

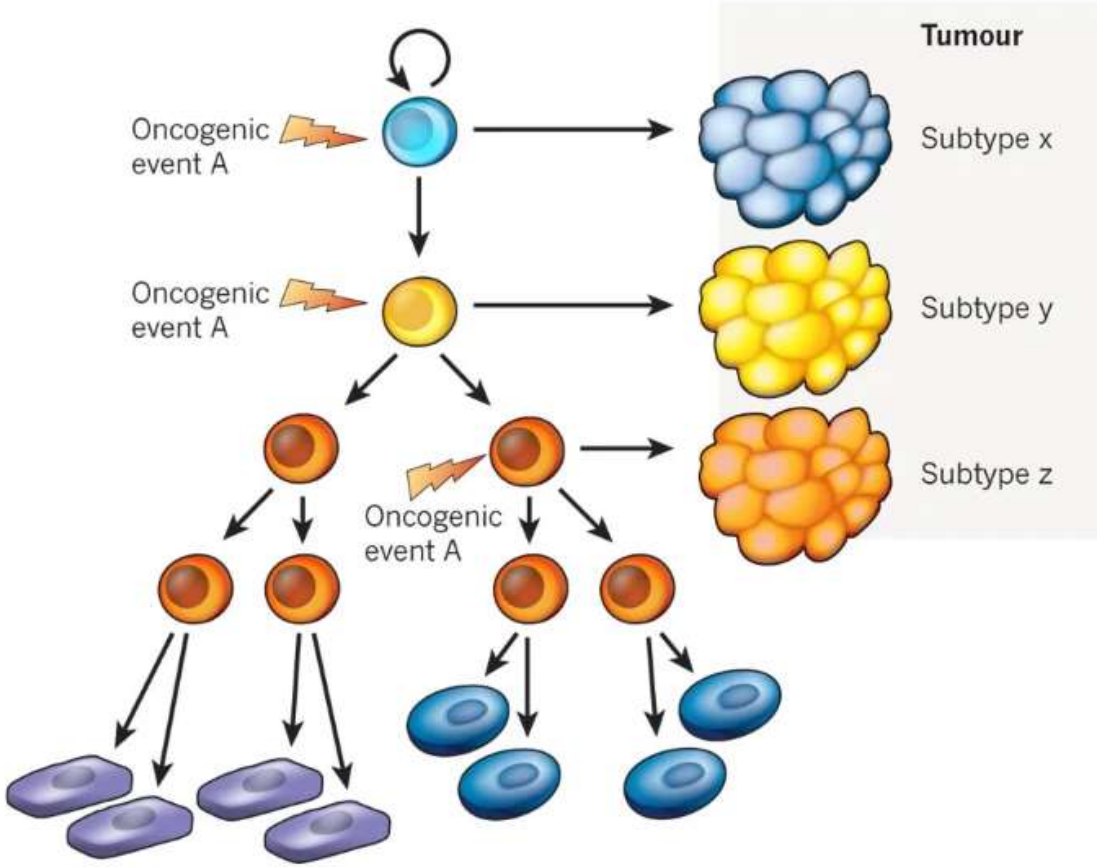
Cellular Differentiation



https://www.science.org.au/curious/epigenetics

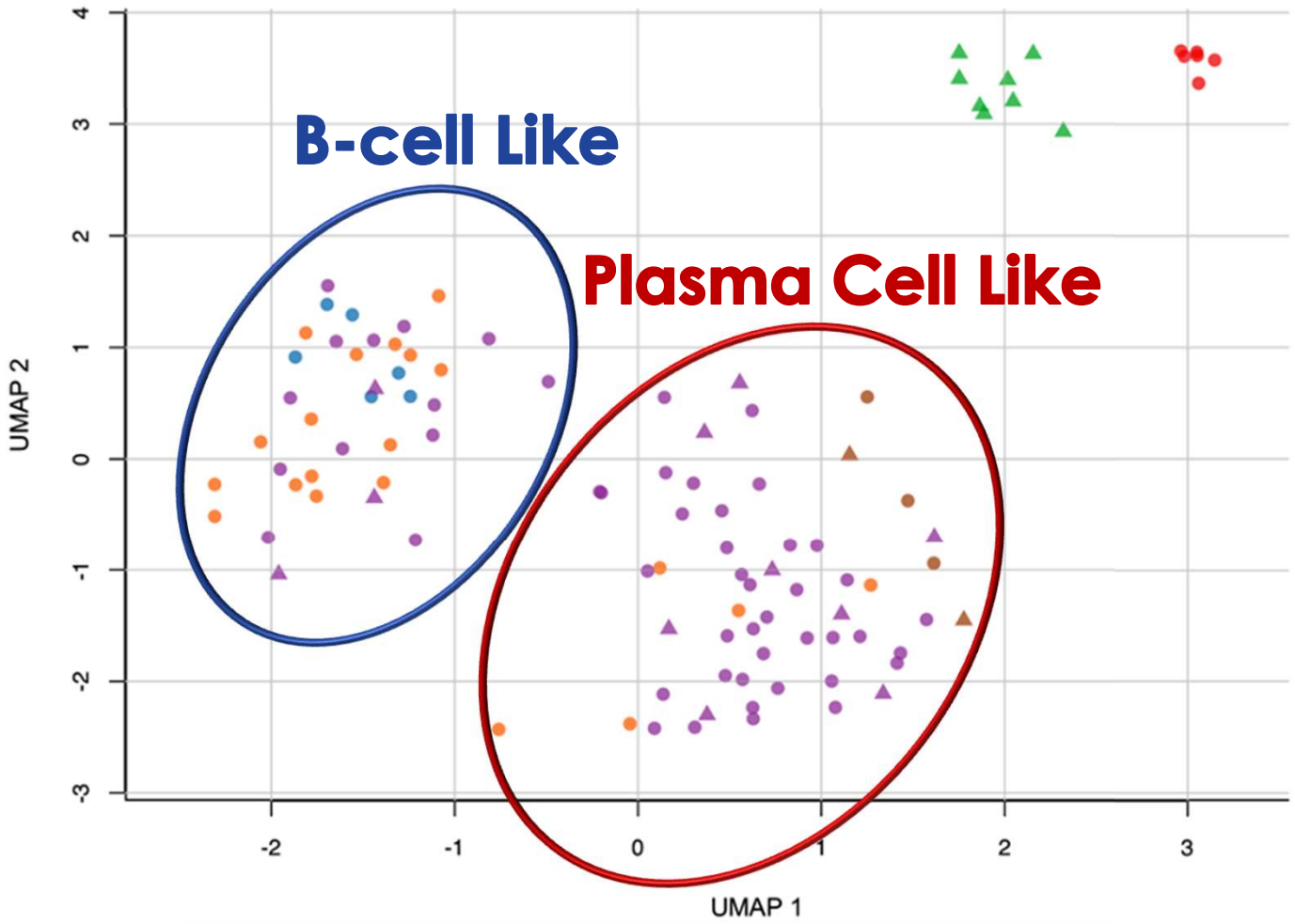
Epigenetic programming from the cell of origin that does not impact the cancer will stay intact providing guidepost to determine the cell type where the cancer first began

The Cell of Origin Model



*Visvader, J. Cells of origin in cancer. Nature **469**, 314–322 (2011)*

Epigenetic Studies in MYD88 Mutated WM



Cell Type
- HD PB
- HD MB
- HD PC
- WM MYD88-Mut/CXCR4-WT
- WM MYD88-Mut/CXCR4-Mut
- WM MYD88-WT
- IgM MM
- Cell Line

Selection
- ● CD19+
- ▲ CD138+
- ◆ Cell Line

Weill Cornell
Ari M Melnick
Epigenomics Core at Weill Cornell
Epigenomics Core

Hunter et al , ASH 2023

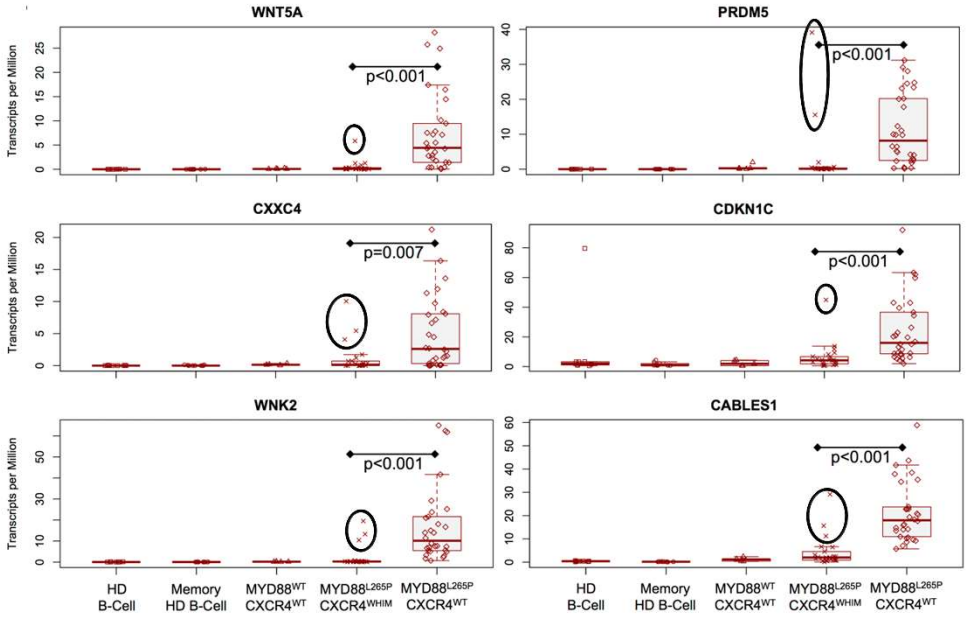
The Bing Center 300-Project: Developing a multi-omic model of untreated WM

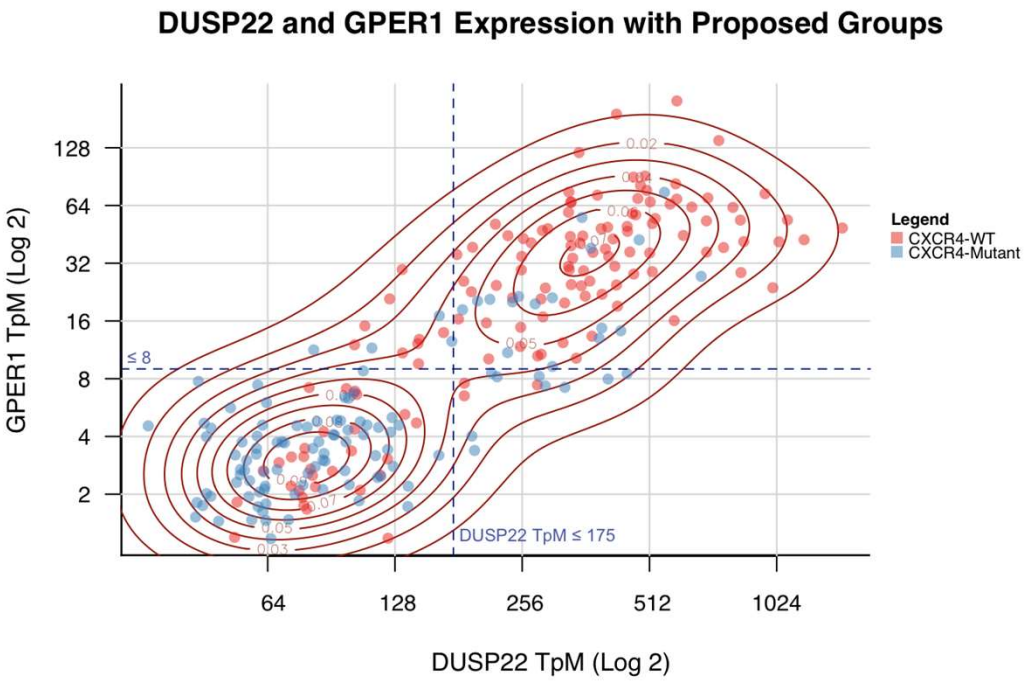
RNASeq was performed on $CD19^+$ bone marrow (BM) samples from 249 treatment-naive WM patients who were MYD88 mutated, as well as 13 paired $CD19^+CD27^-$ and $CD19^+CD27^+$ selected healthy donor (HD) peripheral blood samples. Whole exome sequencing of $CD19^+$ BM cells along with $CD19^-$ peripheral blood mononuclear controls was also performed for 215 of the WM samples.

Metric	Median	Min	Max
Age at Diagnosis (Years)	63	31	91
Bone Marrow Infiltration (%)	50	5	95
HGB	12	3.7	17
IgA	52	5	587
IgG	569	24	4,728
IgM	3,224	104	10,321

Median patient follow up is 8.8 years (range 0.2 - 33.8 years)

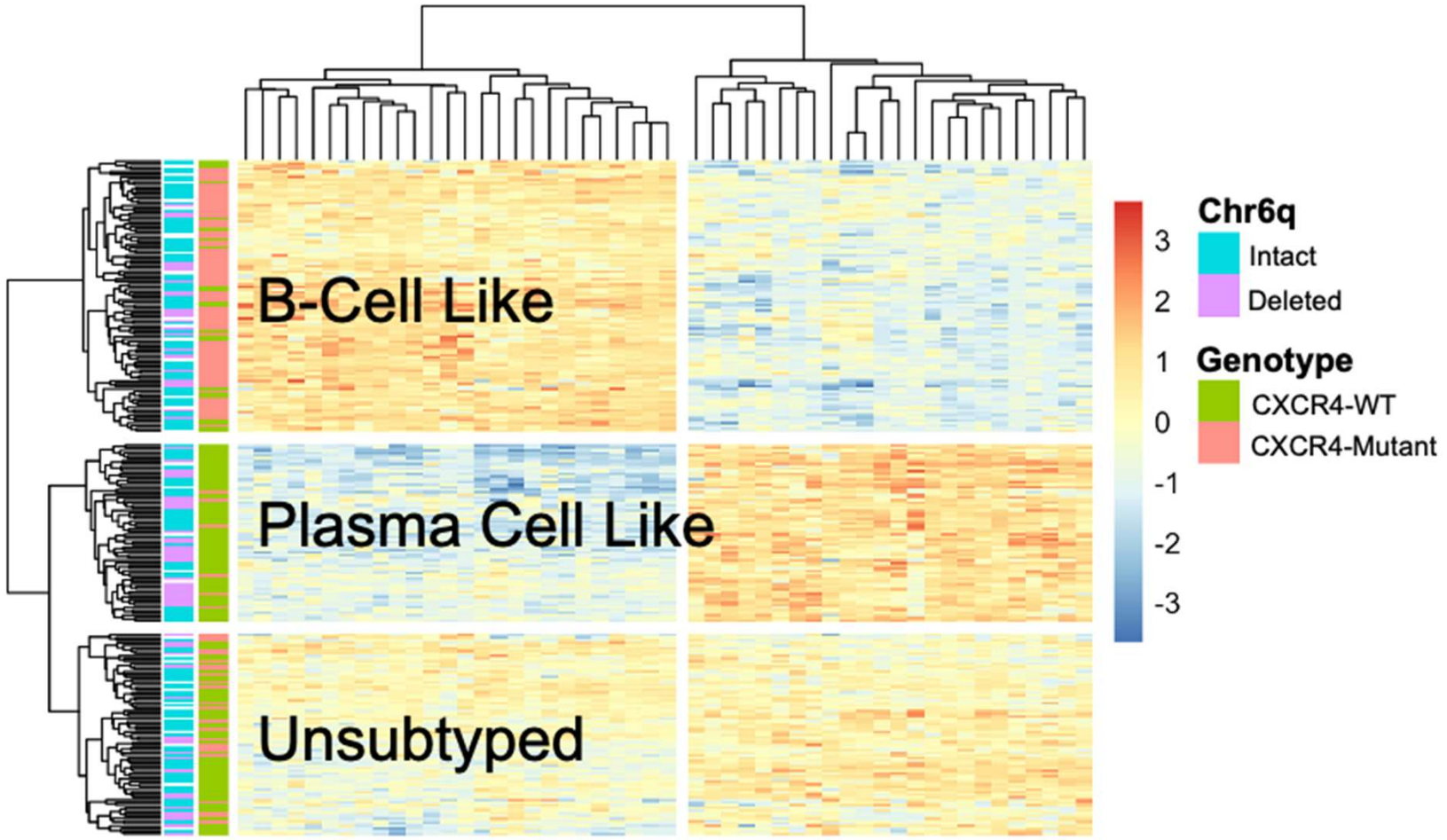
The CXCR4 Mutant Signature: The Chicken or the Egg?





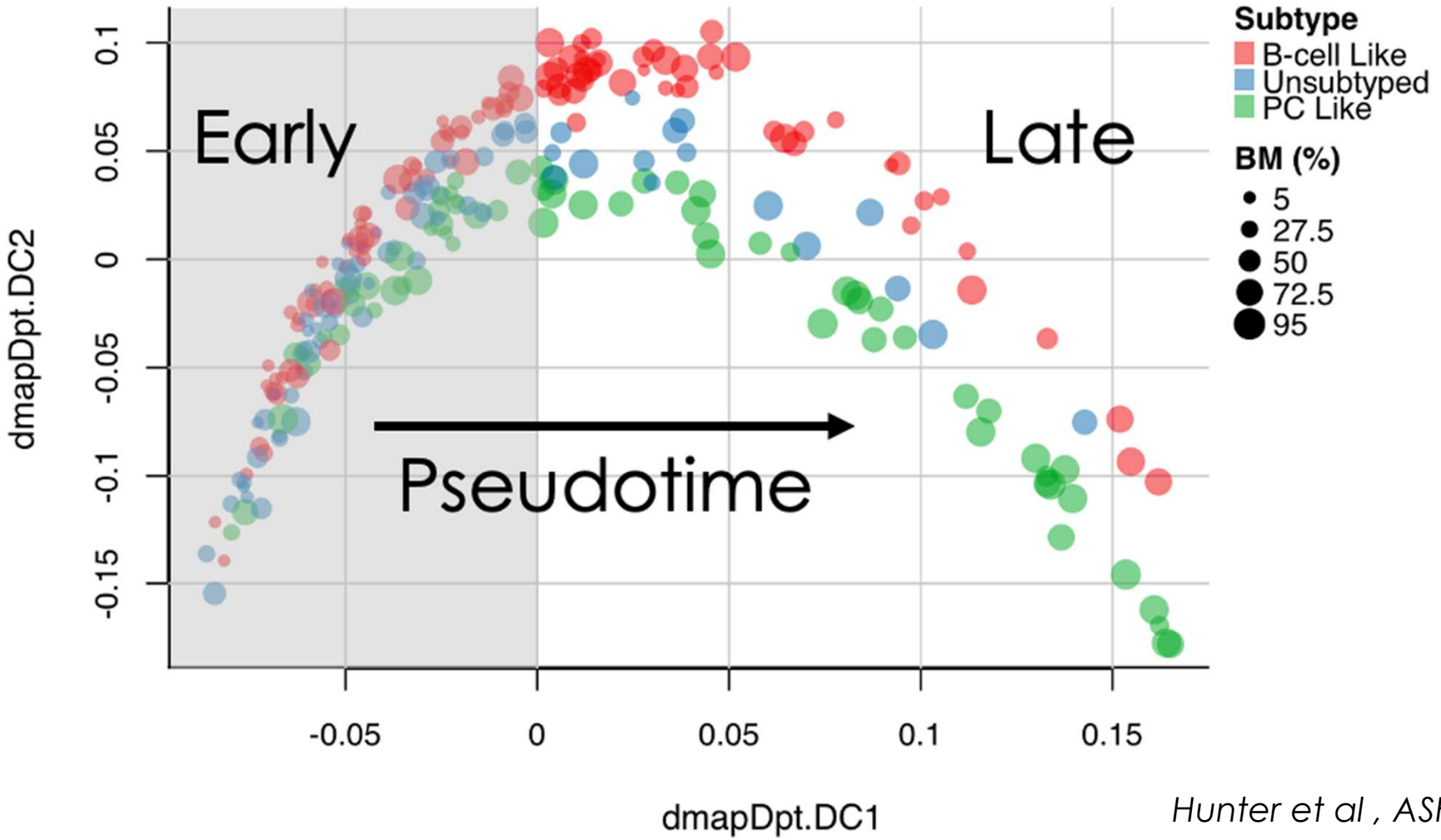
Since there are CXCR4 mutant samples that do not have the signature and CXCR4 wild-type samples which do, can we characterize this signature independent of CXCR4 status?

Clustering WM Samples Based on Gene Expression



Hunter et al , ASH 2022

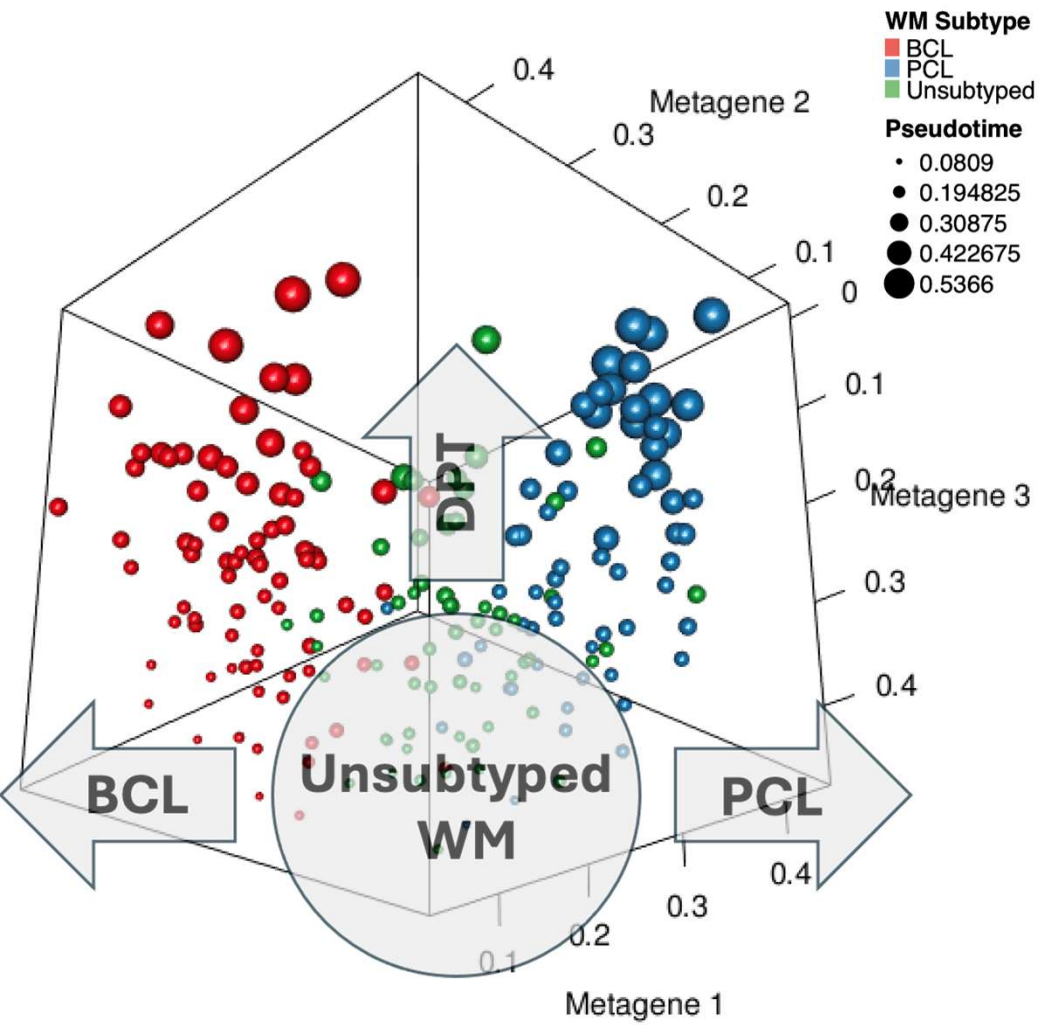
How do WM Cells Evolve Over Time?



Hunter et al , ASH 2022

Hunter et al , ASH 2023

Subtypes of Evolution o WM



Unsubtyped (77/249; 31%)

•Concentrated in early pseudo-time values. More likely to be asymptomatic/Smoldering WM. Appears to evolve into **BCL** or **PCL** over time.

•Intermediate expression of subtype associated genes

B-Cell Like (BCL; 104/249; 42%)

•Subtype associated gene expression regressed to HD levels

•Mutations: CXCR4 (80% vs. 7%), CD79B (9% vs. 3%) , Amp Chr18q (16% vs. 2%)

•Immunophenotype: CD5 (18% vs. 6%)

Plasma Cell Like (PCL; 68/249; 27%)

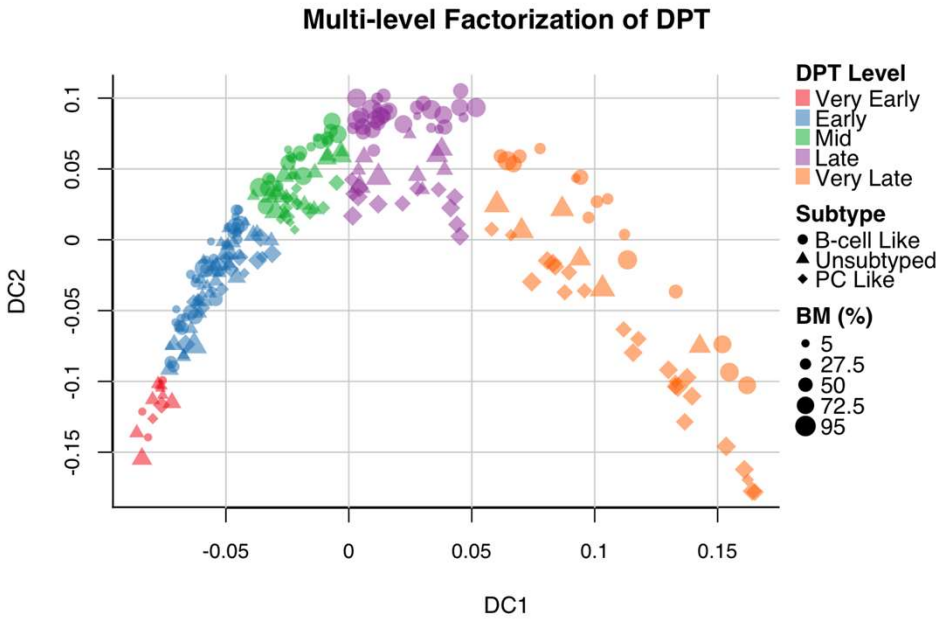
•Subtype associated gene expression becomes more extreme relative to HD levels

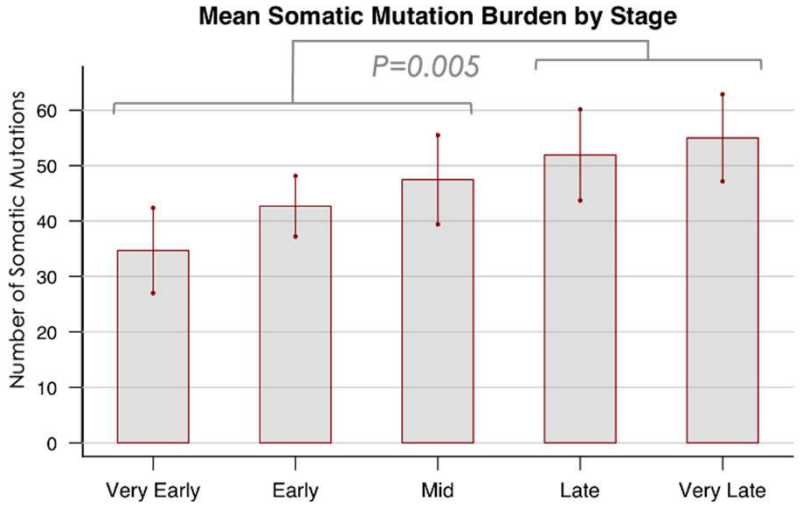
•Mutations: NOTCH1 (9.5% vs. 1.1%), EP300 (18% vs. 5%), Amp Chr6p (18% vs. 3%) , Del Chr6q (46% vs 28%), Del Chr17p (10% vs. 0%)

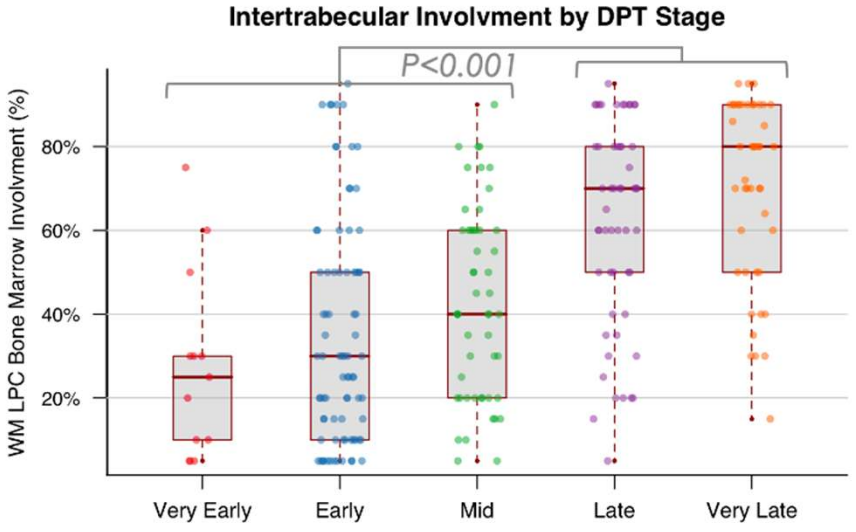
•Immunophenotype: CD10 (12% vs. 1%)

•Clinical Presentation: WM BM Involvement (70% vs. 40%)

Understanding the Transition from IgM MGUS and Smolder in Symptomatic Disease

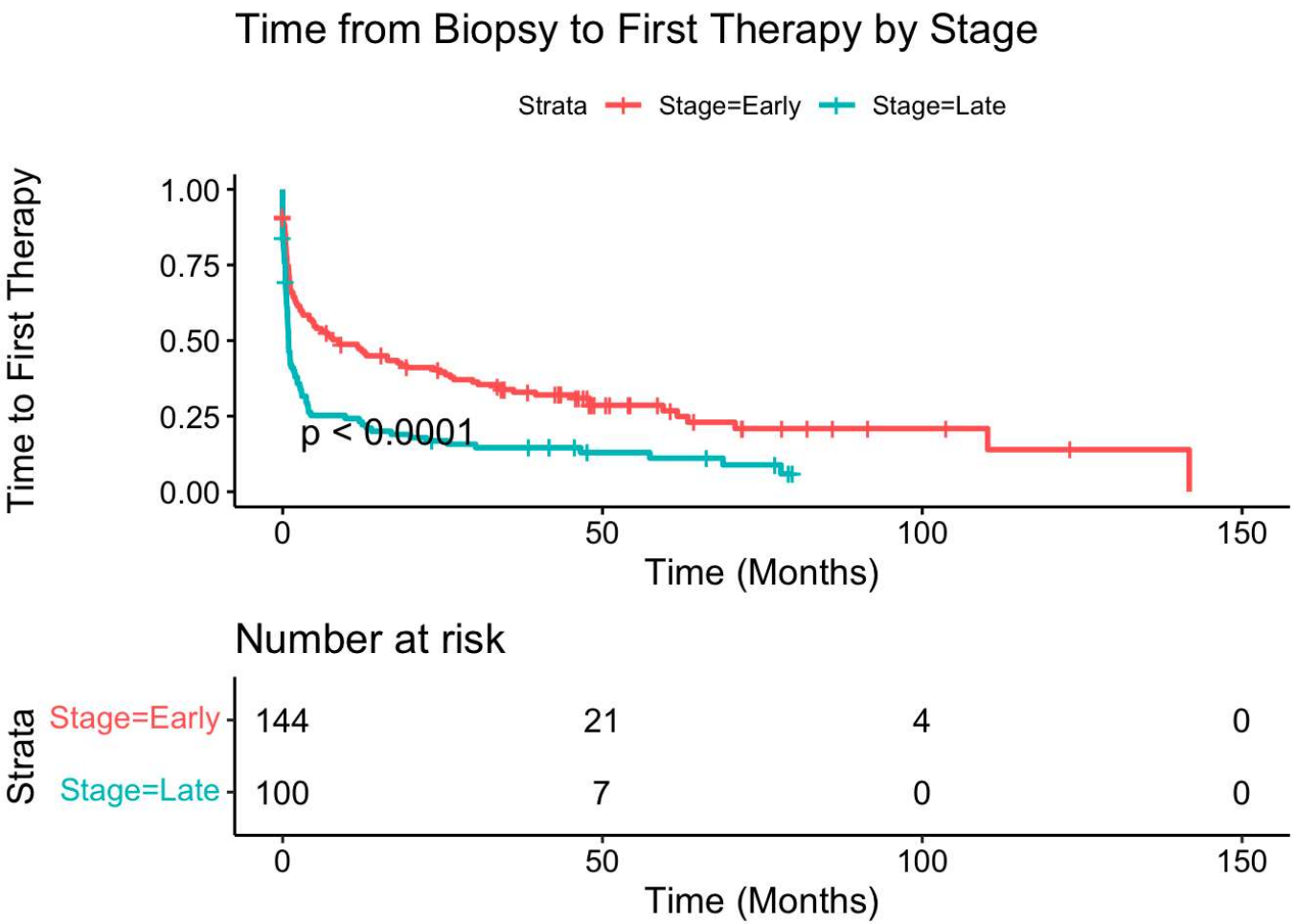






Hunter et al , ASH 2023

Predicting Time to First Therapy



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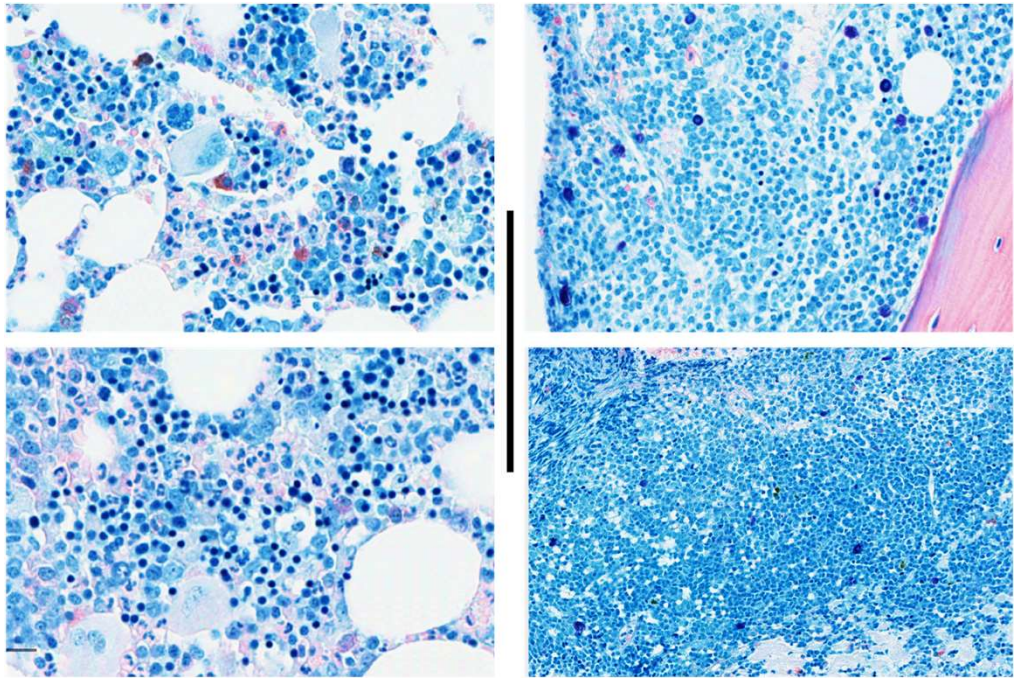
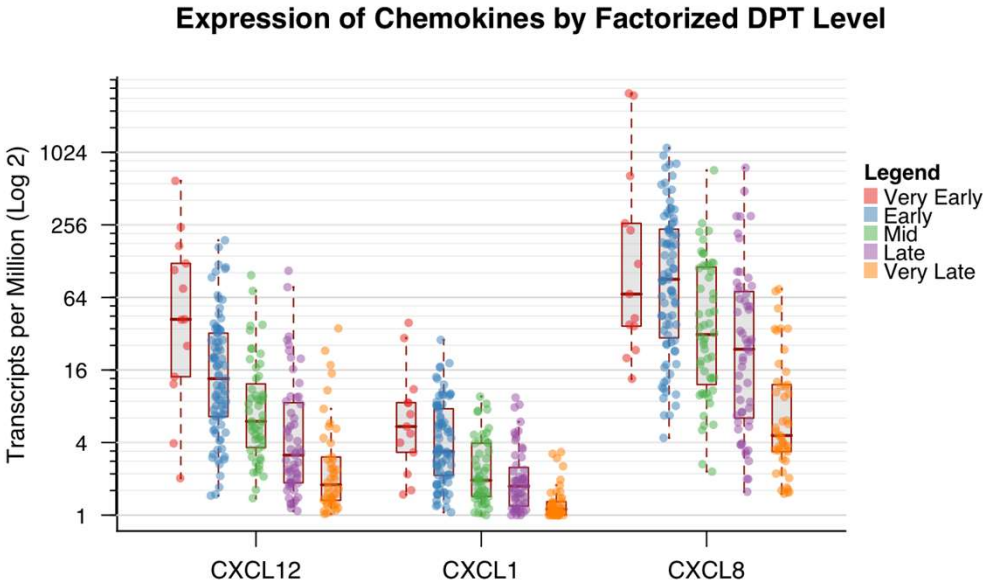
Changes in the Bone Marrow

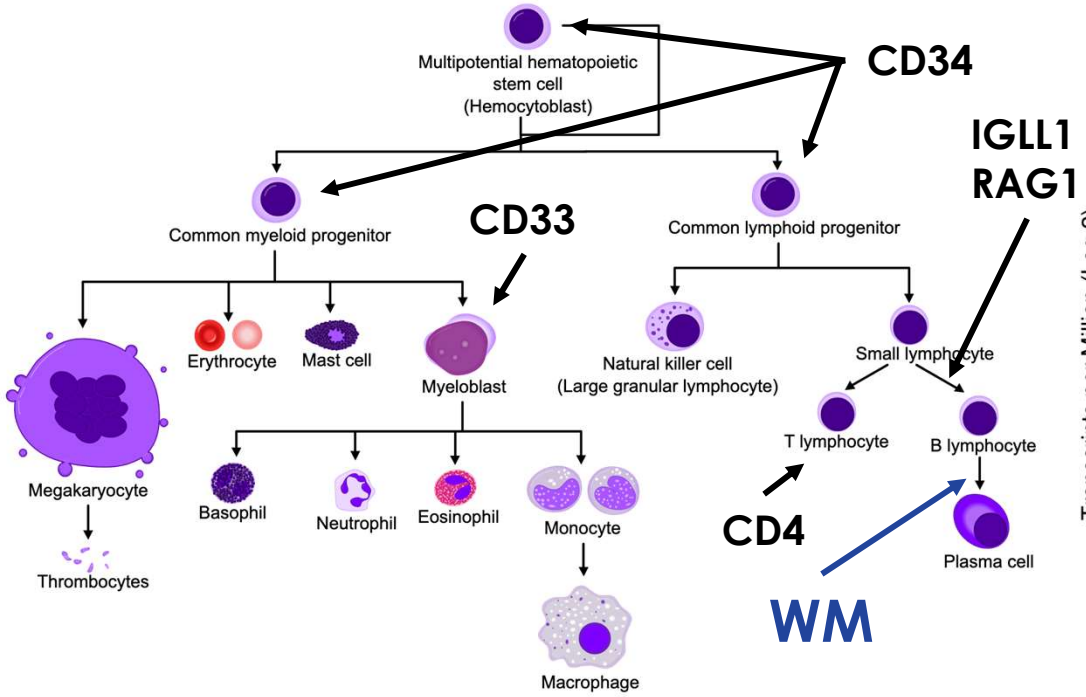
Early Pseudotime **Late Pseudotime**

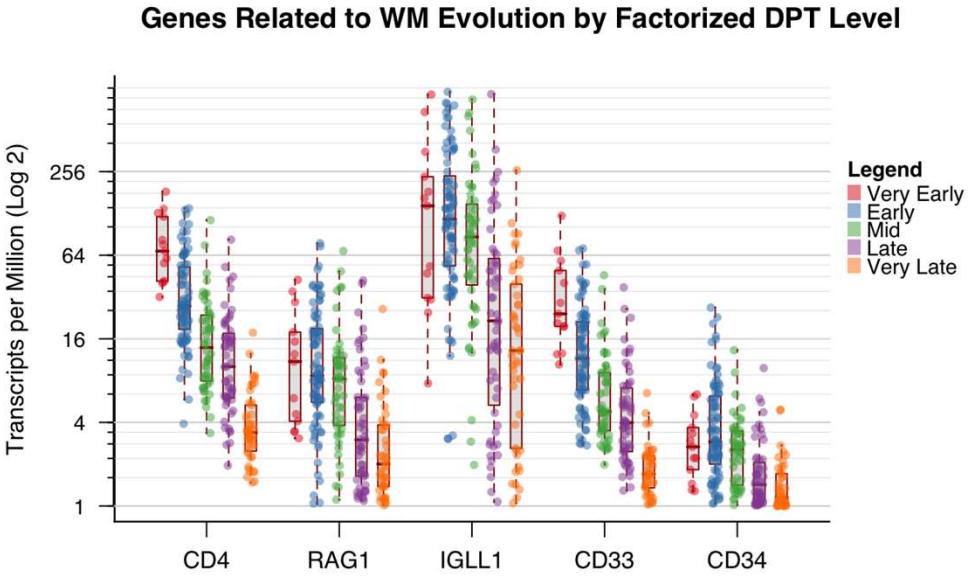




Hunter et al , ASH 2023

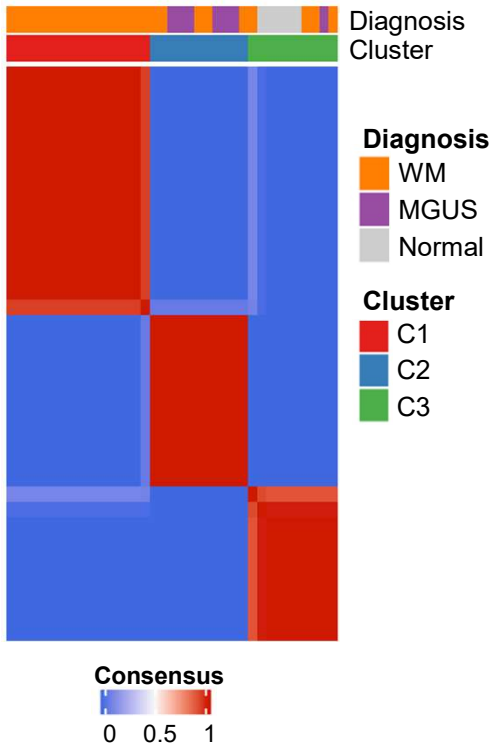
Putting it all together

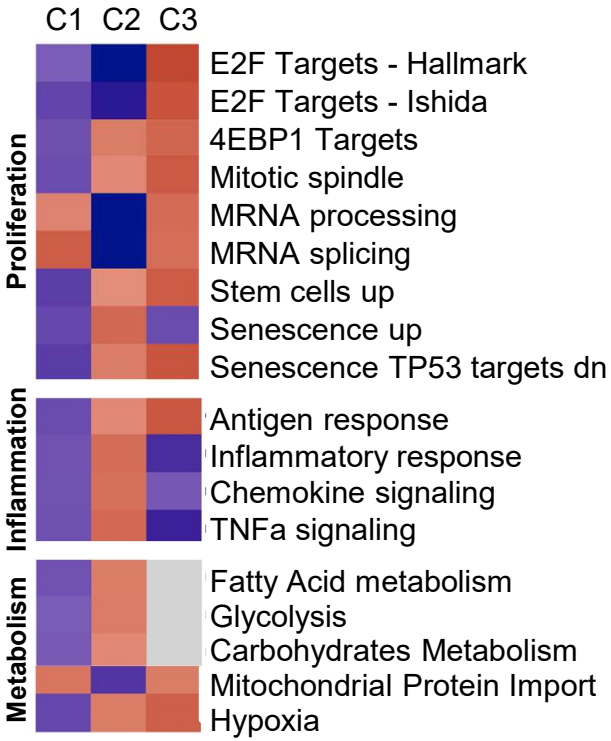


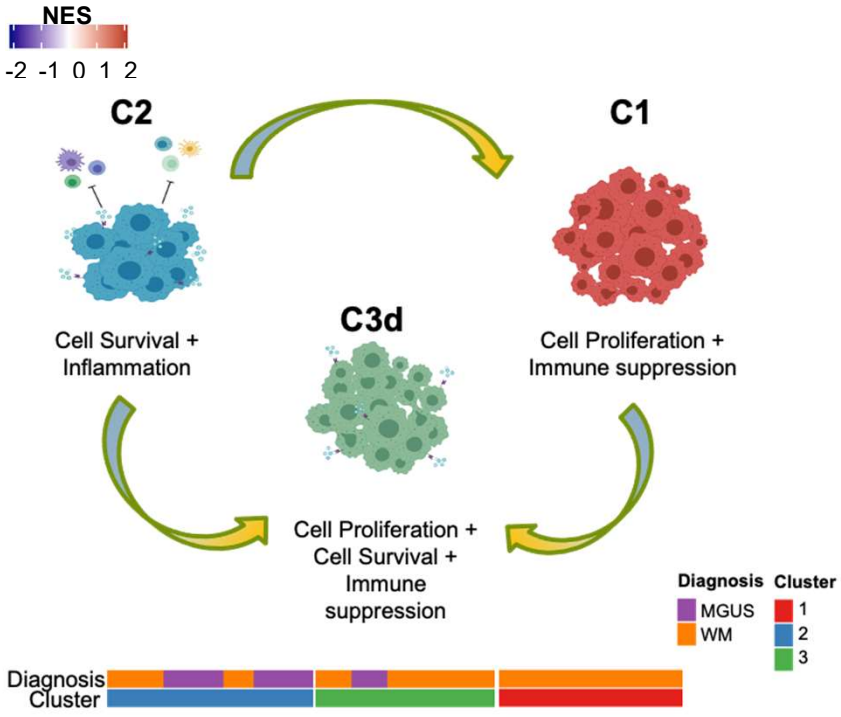


Simplified hematopoiesis By A. Rad and M. Häggström. CC-BY-SA 3.0 license.

Molecular Subtype and Clustering Studies at the Mayo Clinic







Mondello, et al. Front Genet 2022
Mondello, et al. Clin Cancer Res 2023

MAYO CLINIC

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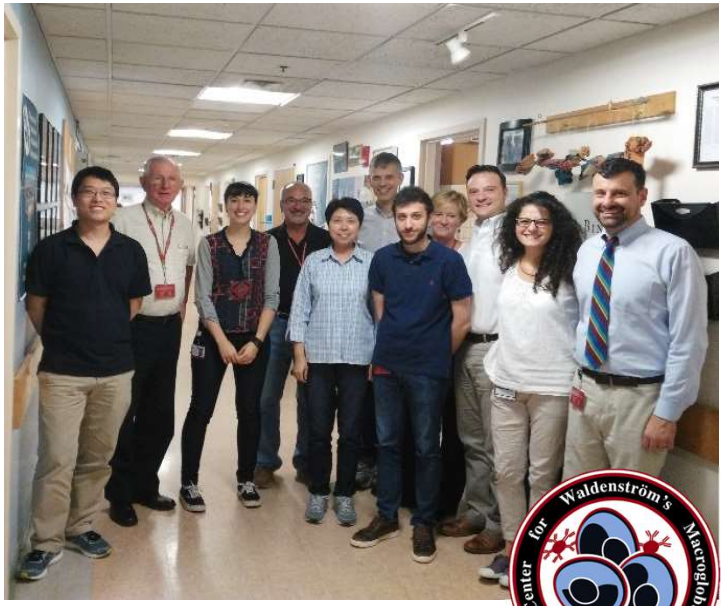
- D'Amato Family Fund for Genomic Discovery
- Leukemia and Lymphoma Society
- NIH Spore Development Award
- ASH Scholar Award
- LLS/IWMF Strategic Roadmap grant



Bing Center for WM

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