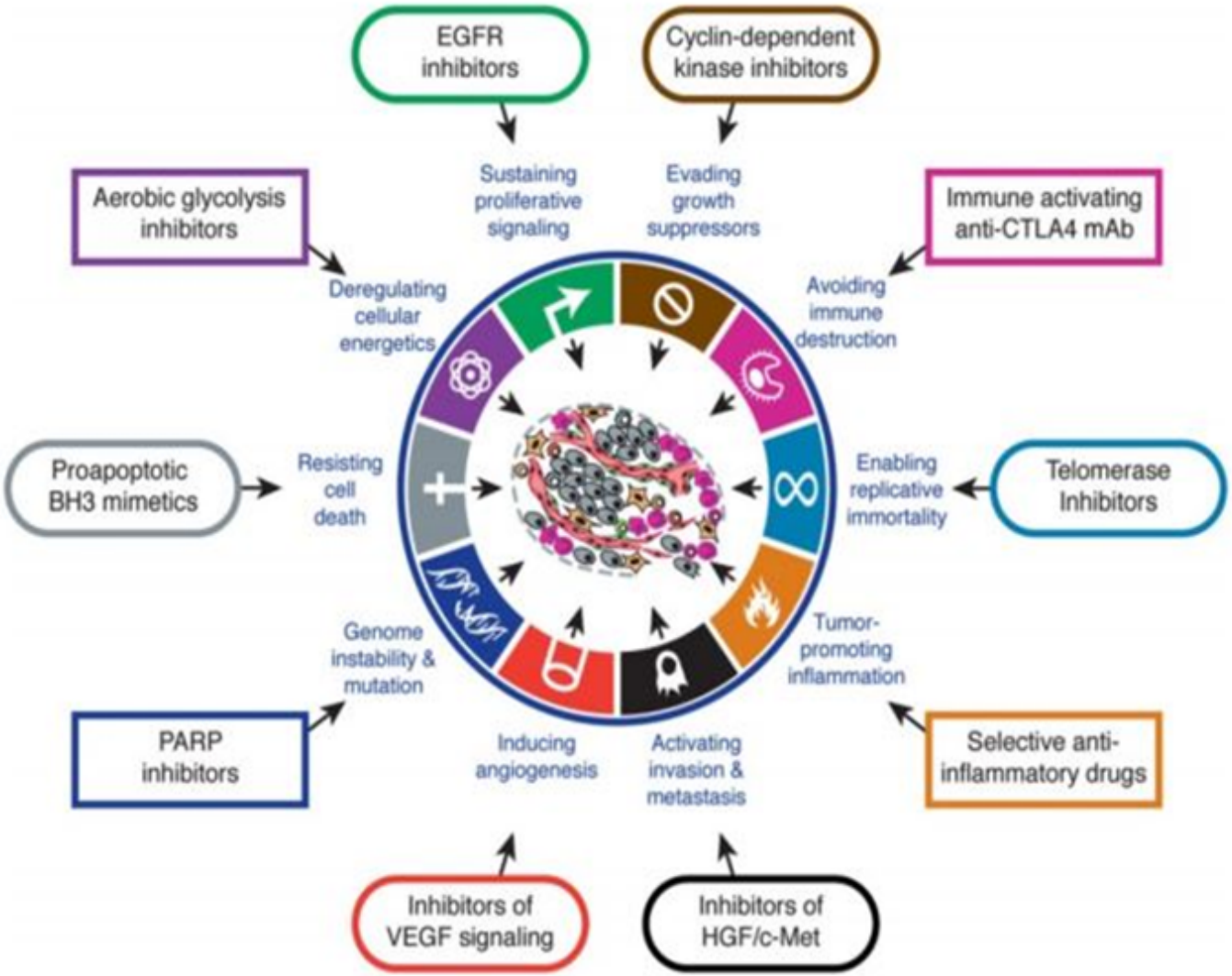
A Basic Science Update: What's New and Exciting on the Horizon?

Cellular and Molecular Complexity of Cancer

As refined by Douglas Hanahan and Robert Weinberg in 2011

Cellular and Molecular Complexity of Cancer



OUTLINE

1. Model Organisms: discovery and testing cancer mechanisms

2. Genomics: Single Cell Sequencing

3. Bringing tools together with Big Data: Deep Learning Tools

4. Structural Biology: CryoEM leads small compound design

5. Technology meets Application: CRISPR

6. Immune Oncology: Immunotherapy, CAR-T and more …

OUTLINE

1. Model Organisms: discovery and testing cancer mechanisms

2. Genomics: Single Cell Sequencing

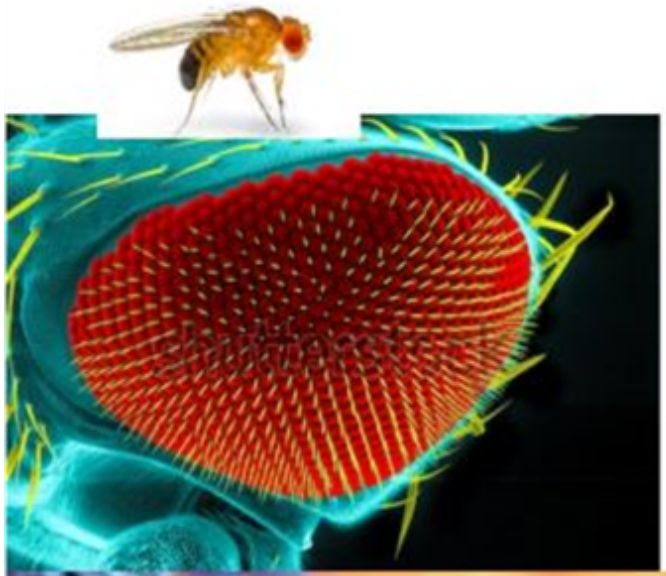
3. Bringing tools together with Big Data: Deep Learning Tools

4. Structural Biology: CryoEM leads small compound design

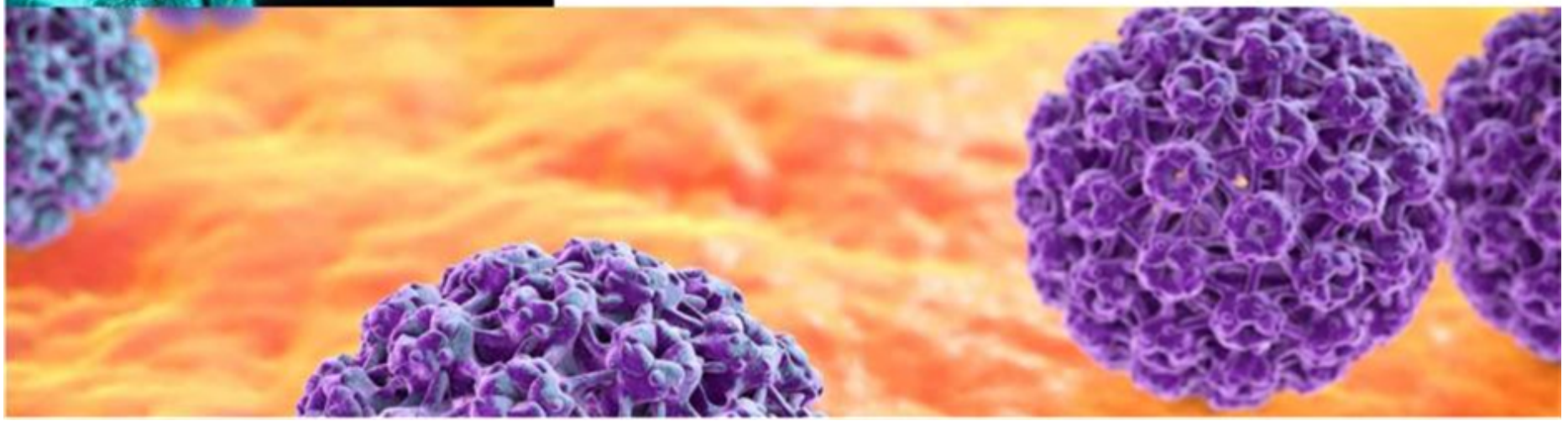
5. Technology meets Application: CRISPR

6. Immune Oncology: Immunotherapy, CAR-T and more …

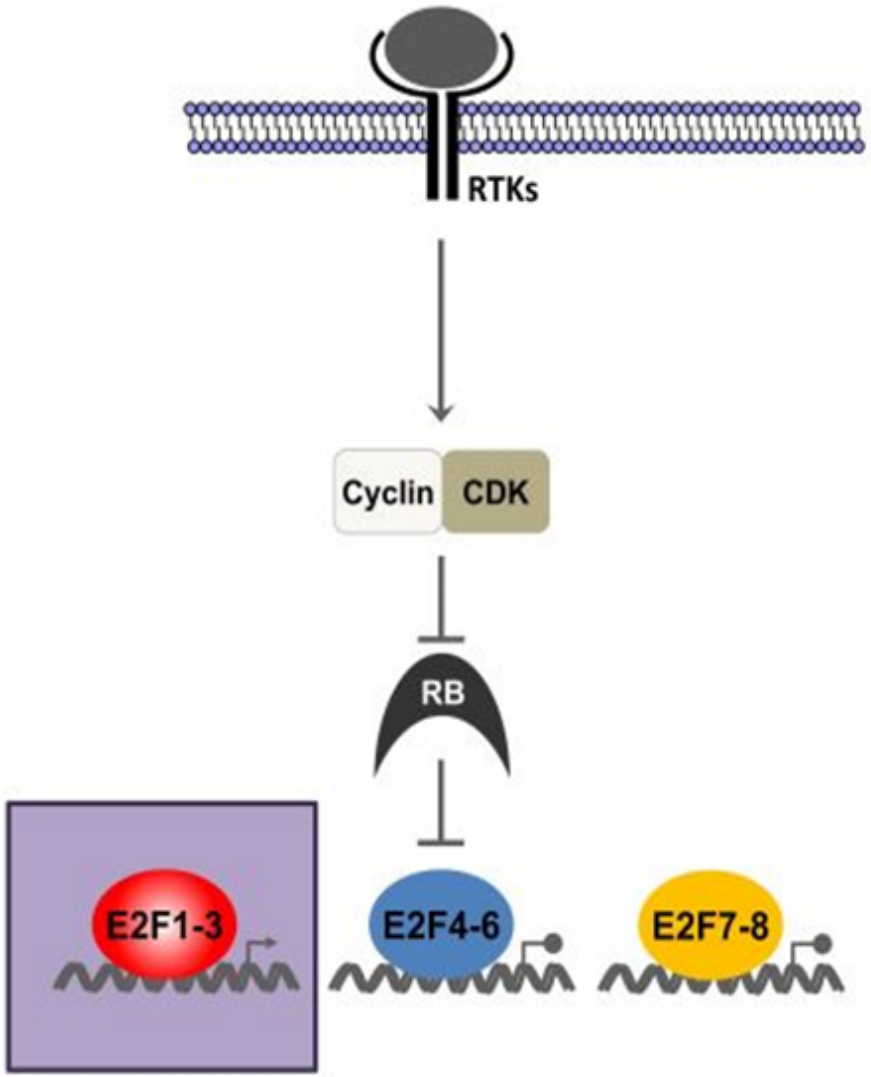
1. Model Organisms in Biology



- Oncogenes
- Tumor Suppressors
- Modifiers



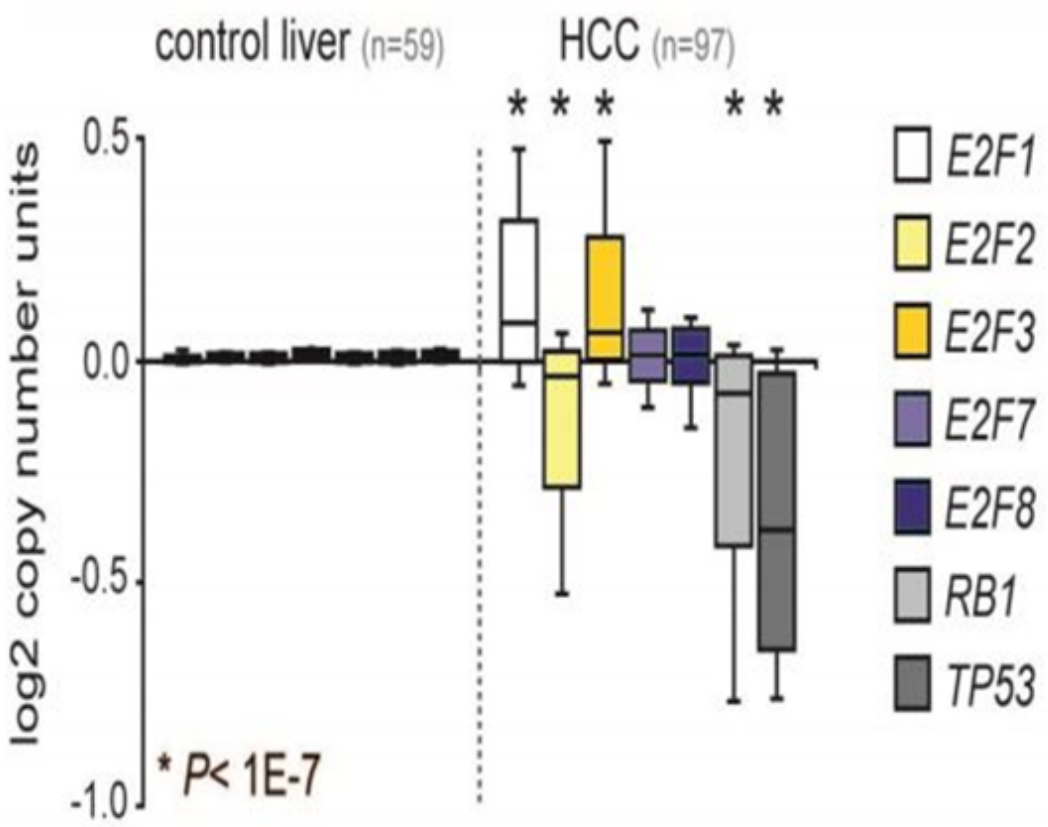
First Tumor Suppressor Ever Identified: RB



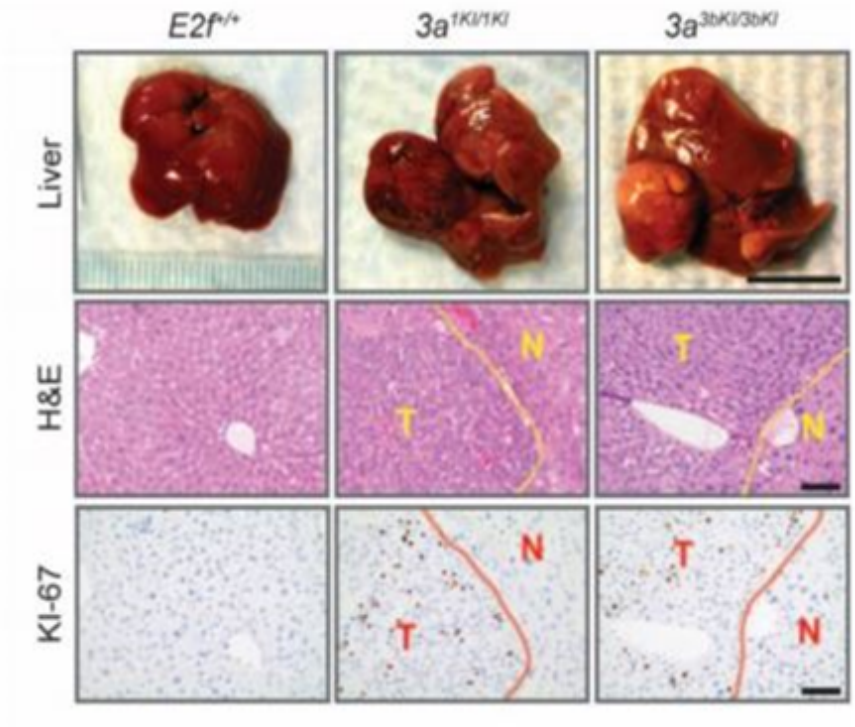
Selected pubs:

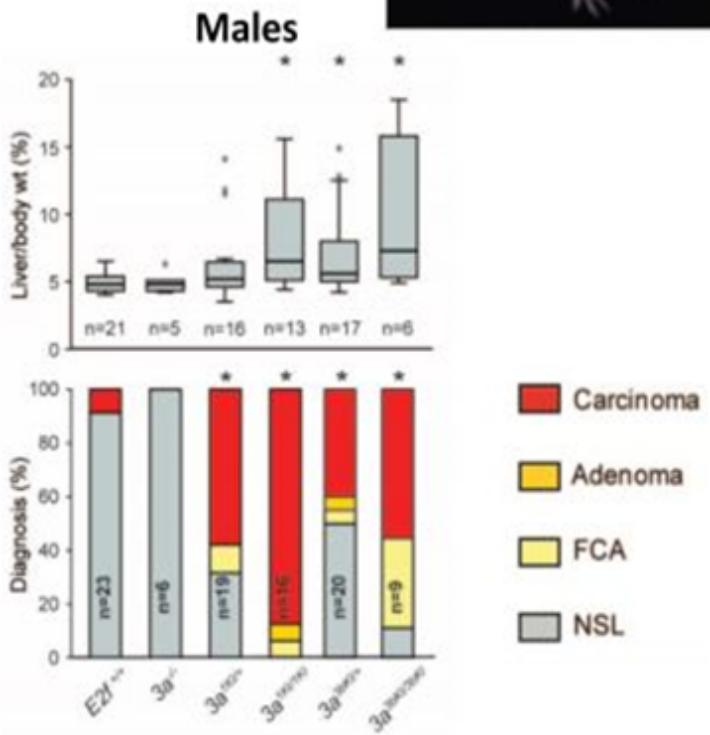
Wu et.al., 2001. Nature
Wu et.al., 2003. Nature
Saavedra et.al., 2003. Cancer Cell
Iavarone et.al., 2004. Nature Genetics
Wenzel et.al., 2007. Gen & Dev
Tsai et.al., 2008. Nature
Chong et.al., 2009. Nature
Chen et.al., 2009. Nature
Chen et.al., 2009. Nature Cancer Rev.
Wenzel et al., 2011. Development
Liu et.al., 2015. Nature Cell Bio.
Jones et.al., 2016. JCI

Subtle copy number gains in *E2F1* and *E2F3* in bladder, ovarian and hepatocellular carcinoma (HCC)



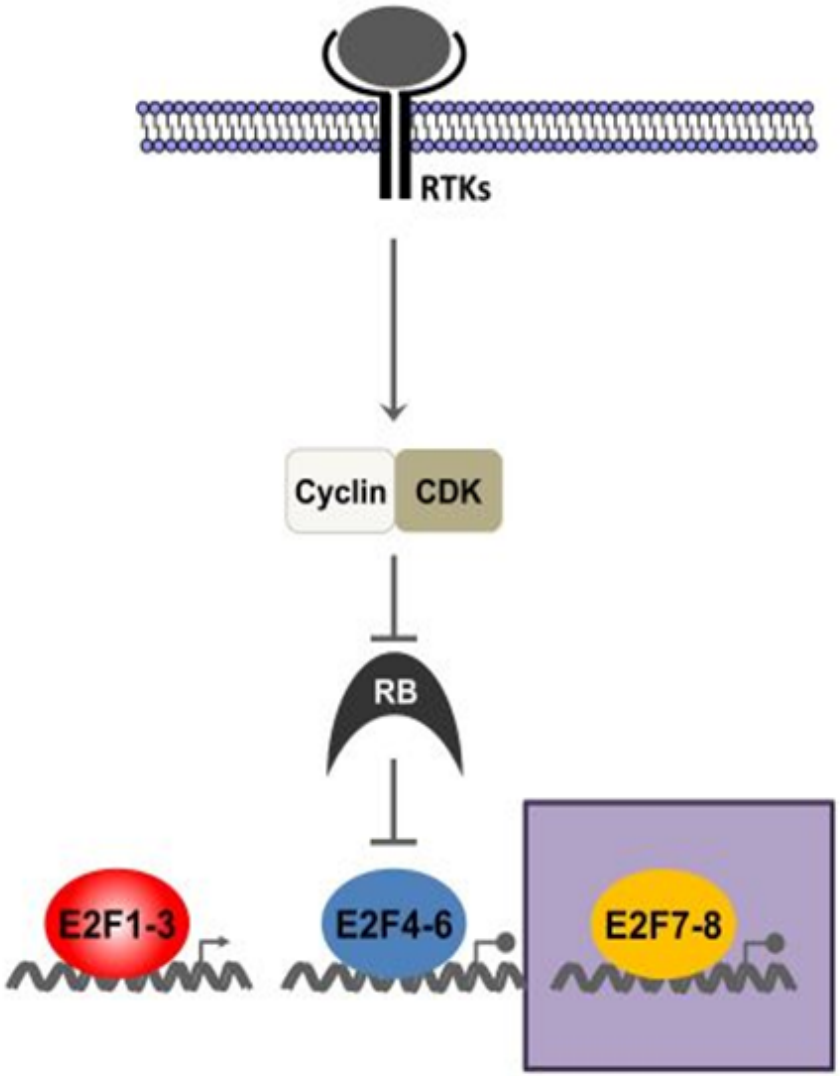
Copy number gains in *E2f1* & *E2f3* leads to hepatocellular carcinoma in mice



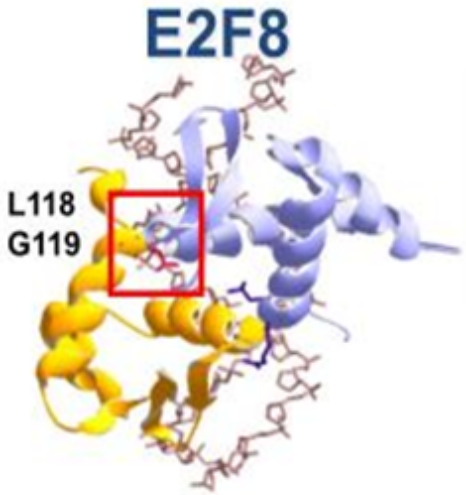


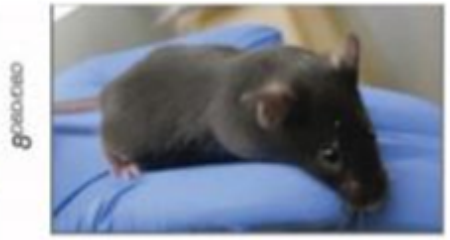
Kent et.al., 2018. JCI.

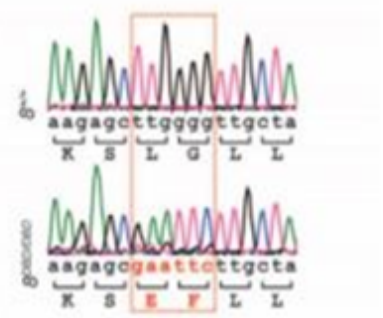
First Tumor Suppressor Ever Identified: RB



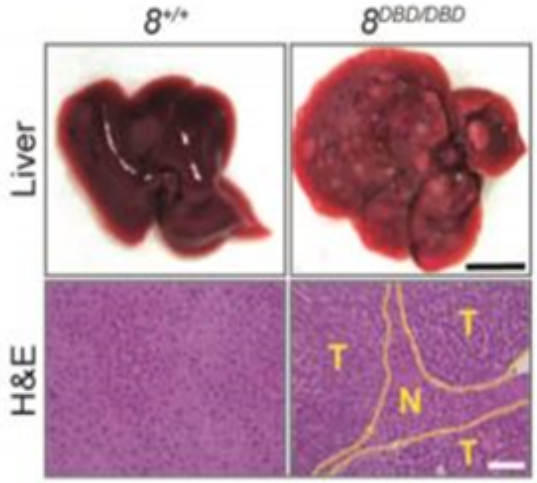
HCC development in E2F8^{DBD} mutant mice

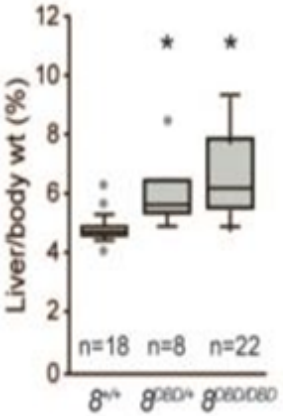


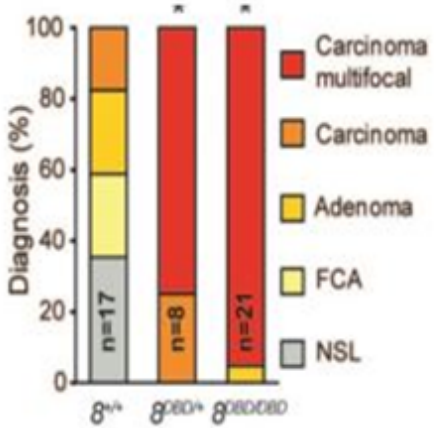




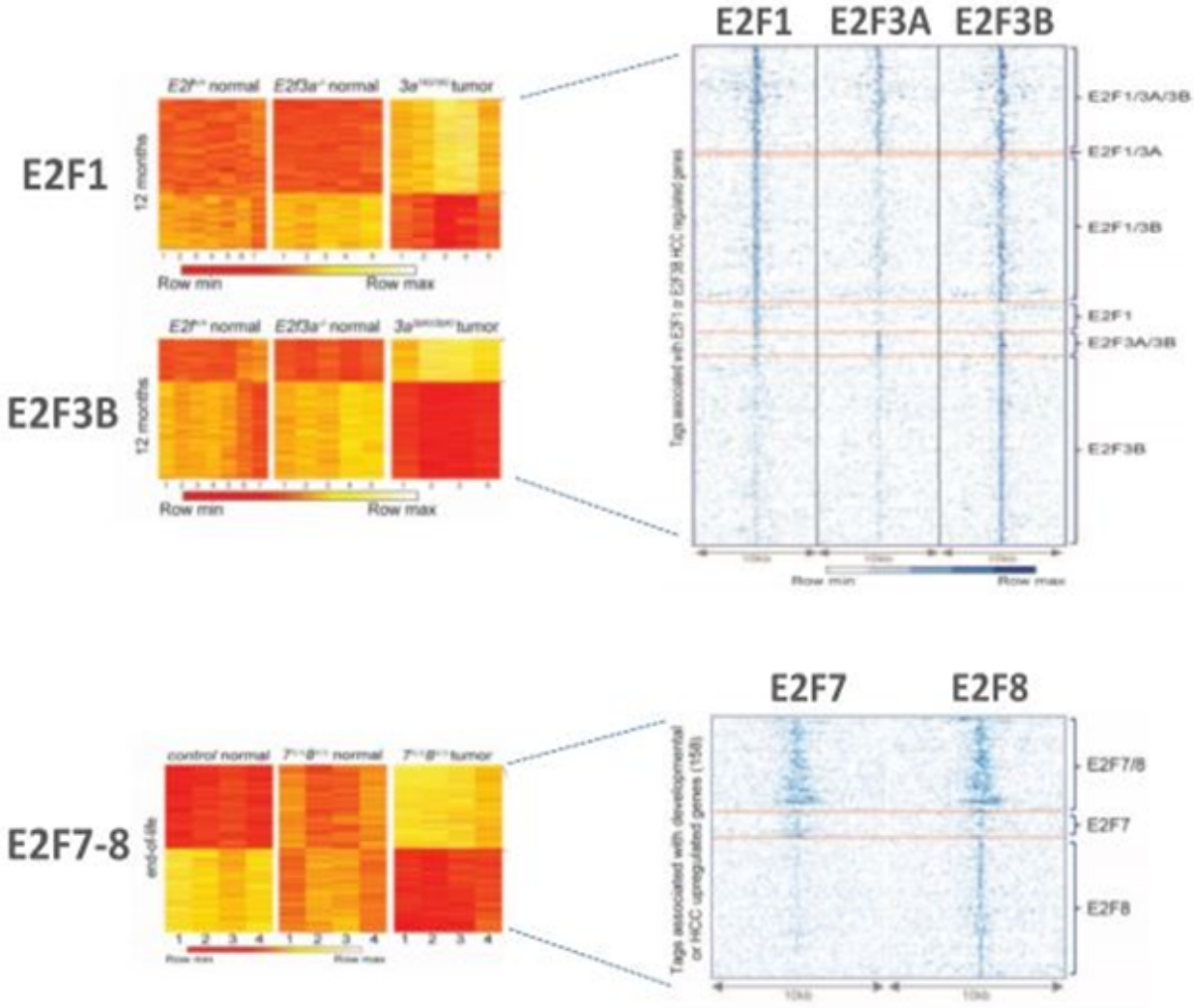
Kent et.al., 2017. JCI.







Expression & Chromatin binding landscape of E2Fs

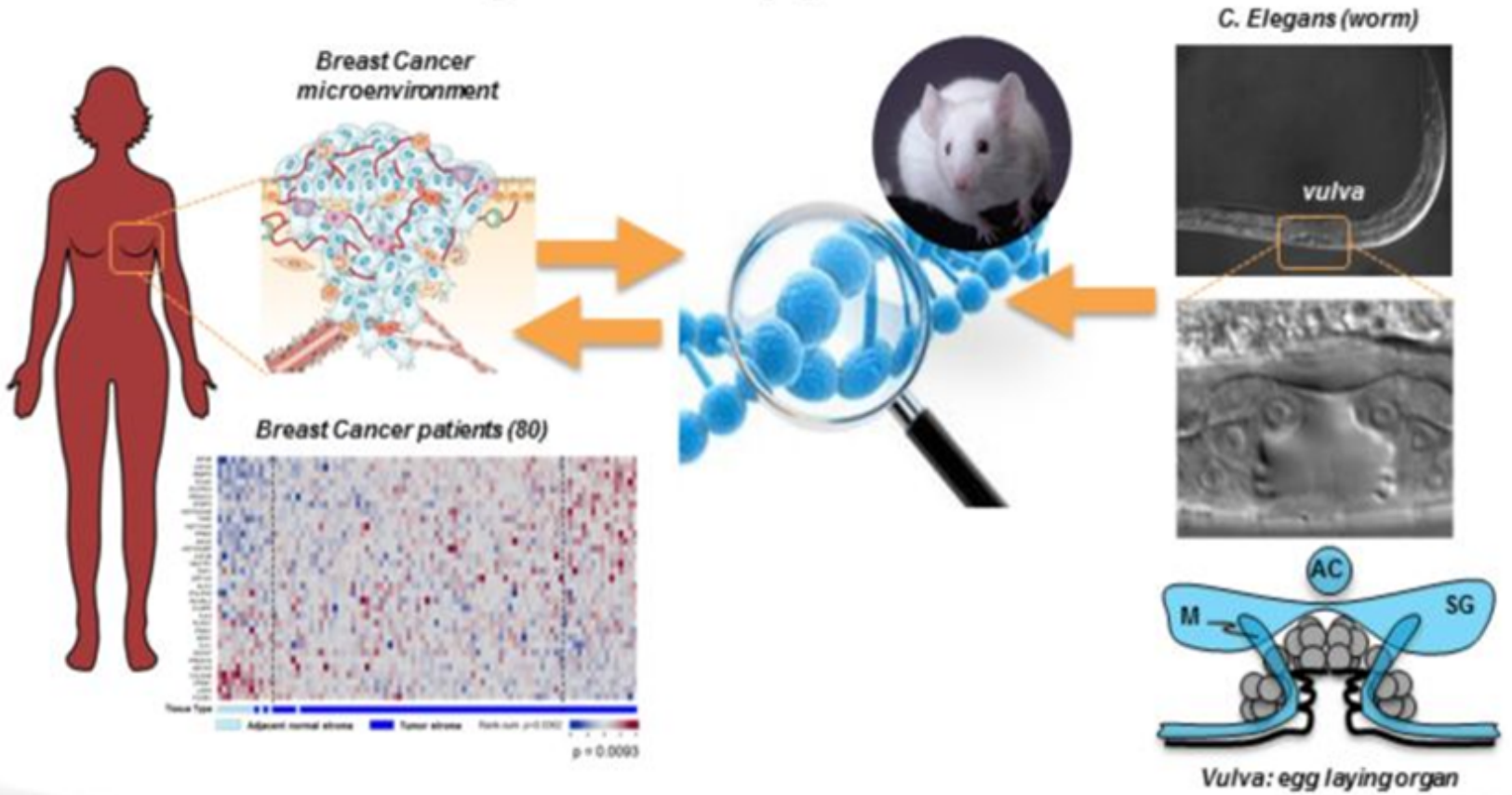


Antagonistic roles of activators and atypical repressors in liver cancer

Oncogenes

Tumor Suppressors

Cross Species Approach to Cancer



Liu et.al., 2017. Dev Cell

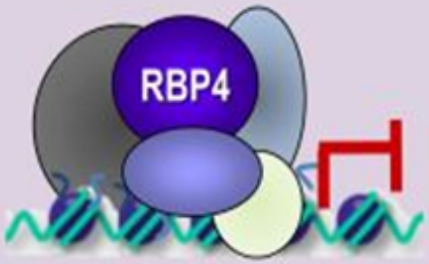
Concerted tumor suppressive pathways in the tumor stroma of breast cancer

Chromatin Remodeling

- H3.3
- H2BF
- H2AB
- H4H

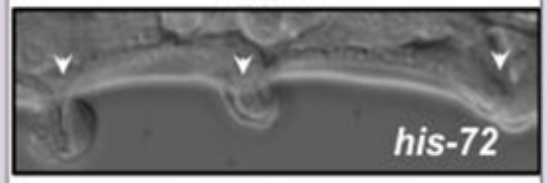
- ASF1/HIRA/

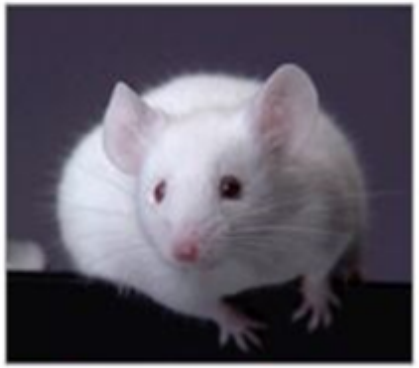
- RUVBL2
- TLK-1/2
- RBBP4
- SCCPDH

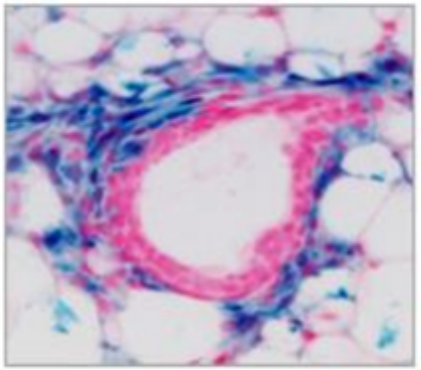


Transcriptional Network

adult

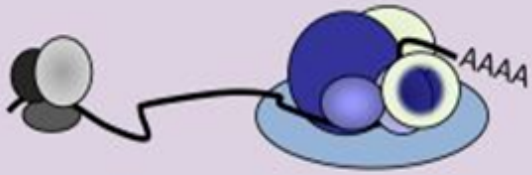






Cyto. PolyAdenylation

- CPEB1
- SYMK1
- PAF1
- NCBP2
- EIF4E



Translational Network

OUTLINE

1. Model Organisms: discovery and testing cancer mechanisms

2. Genomics: Single Cell Sequencing

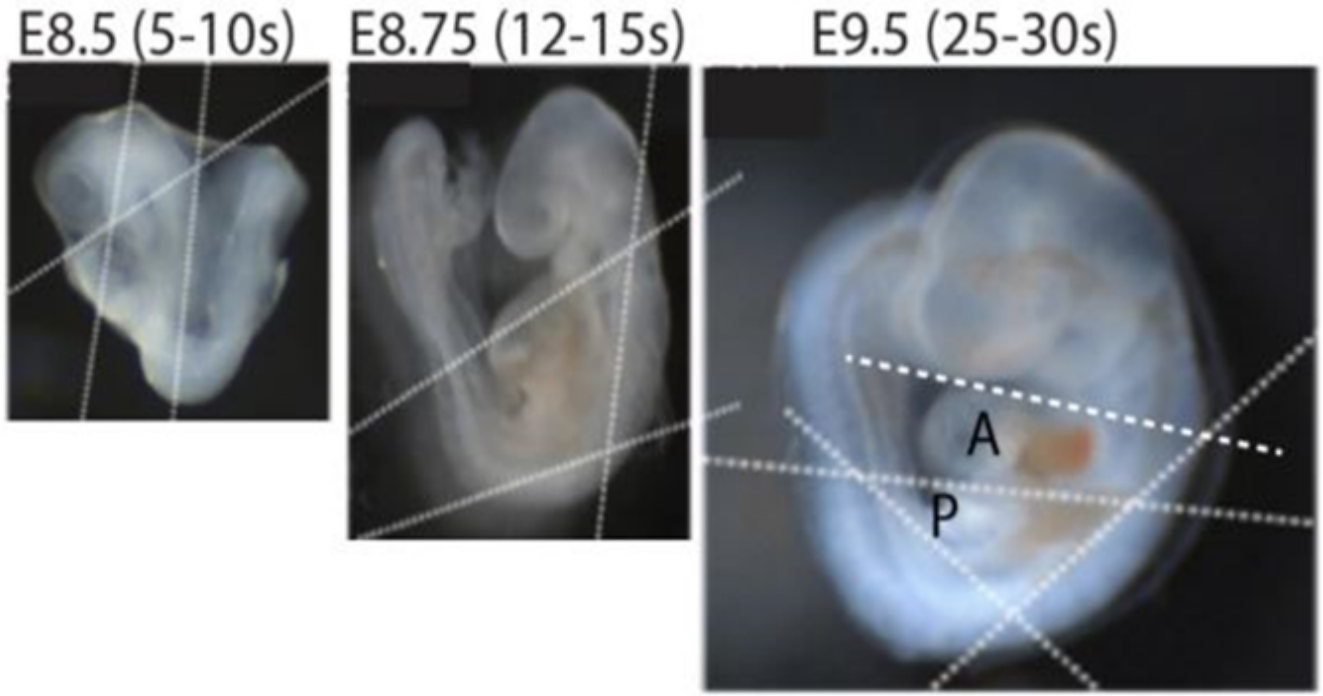
3. Bringing tools together with Big Data: Deep Learning Tools

4. Structural Biology: CryoEM leads small compound design

5. Technology meets Application: CRISPR

6. Immune Oncology: Immunotherapy, CAR-T and more …

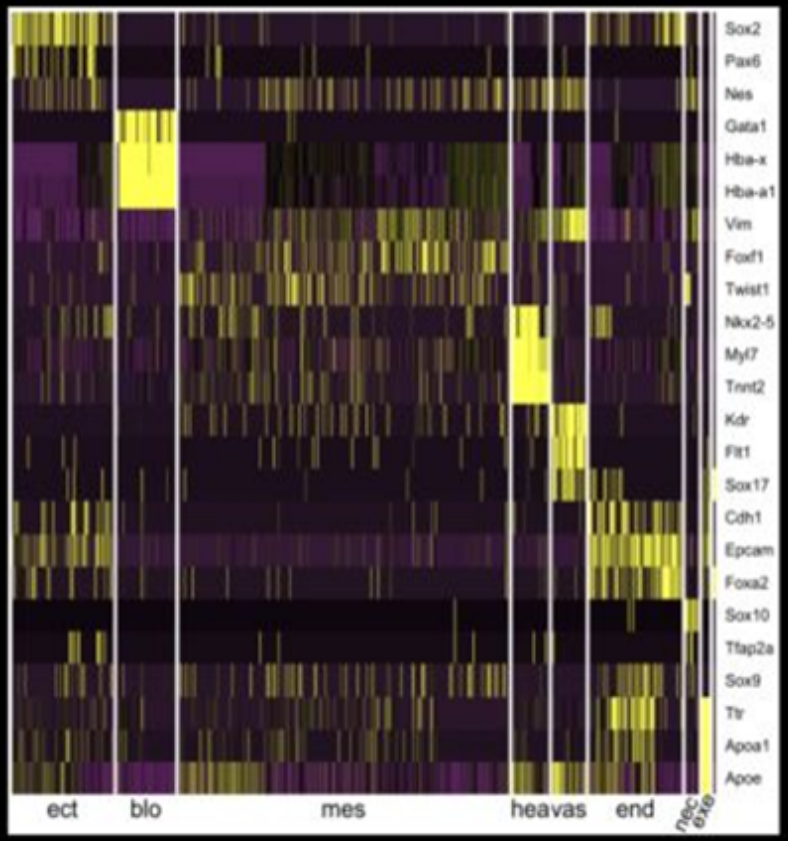
2. Genomics: Single Cell Sequencing

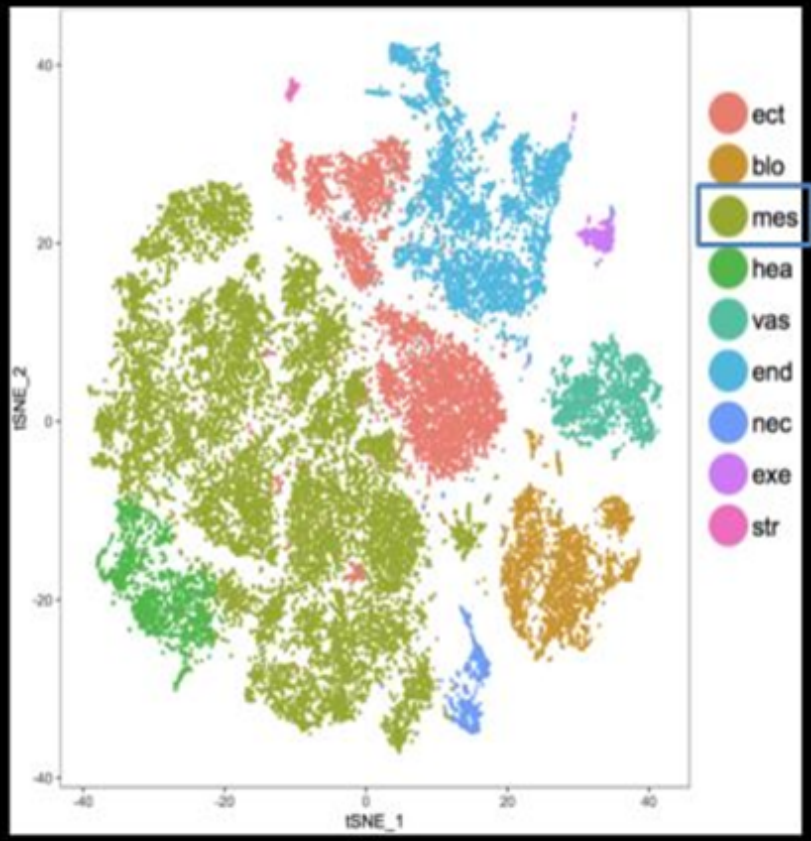


10X Genomics Drop Seq
31,000 cells

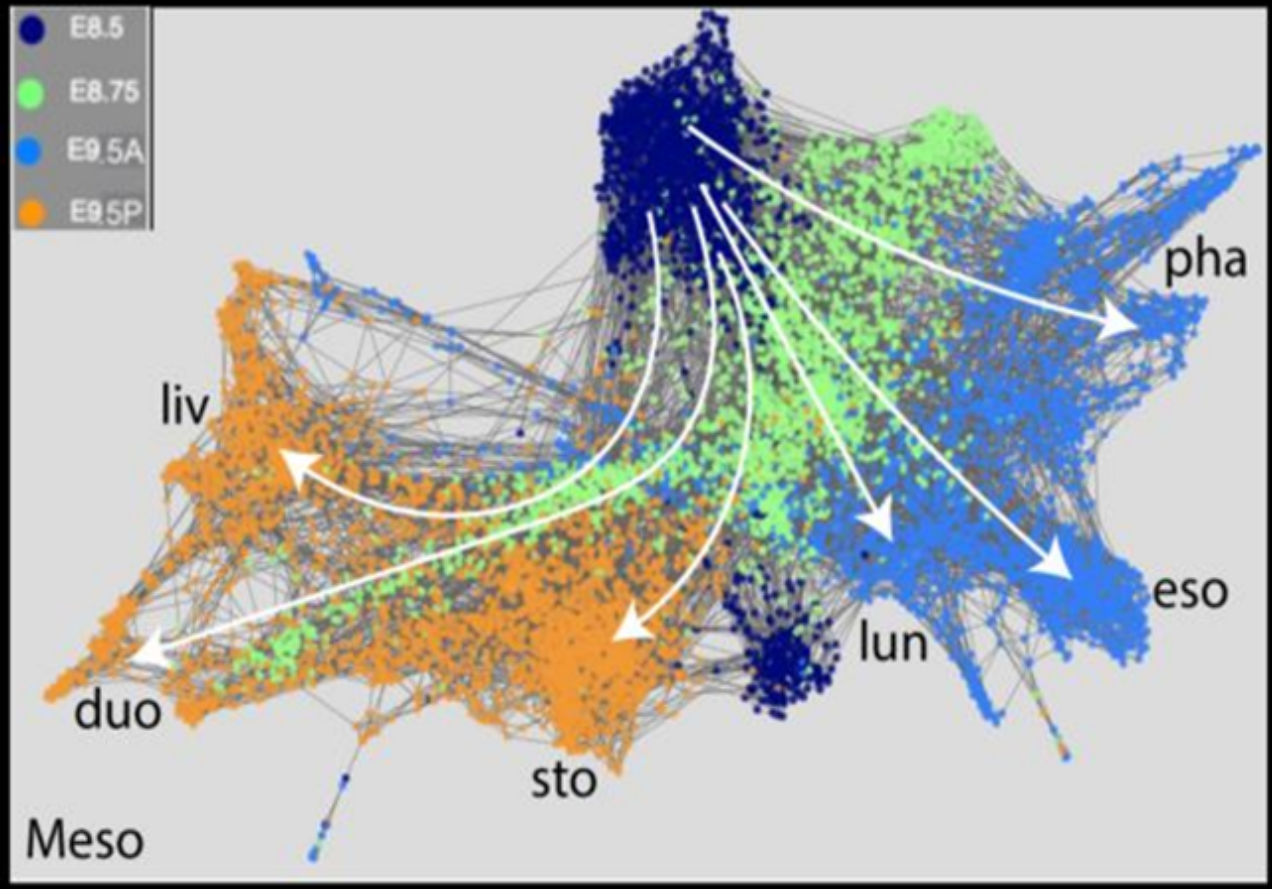
Han et.al., 2019. Per. Comm.

Unsupervised Clustering of Single Cells Based on Transcriptome Similarity

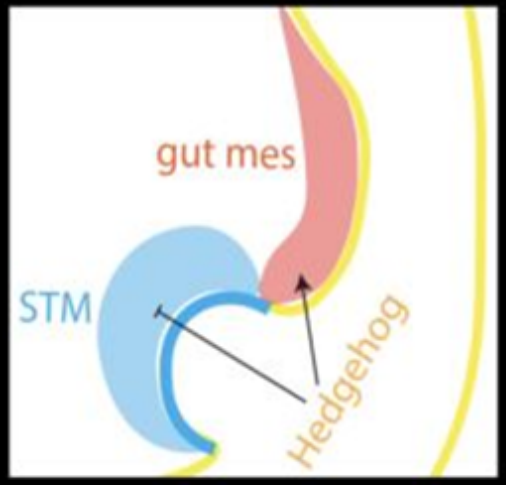




In silico Modeling the Lineage Diversification of the Splanchnic Mesenchyme



Summary



- Regional Patterning of the anterior splanchnic mesenchyme
- Function of Hedgehog activity in patterning the STM or the gut tube mesenchyme
- Tumor Cell of Origin, Evolution and Heterogenecity

OUTLINE

1. Model Organisms: discovery and testing cancer mechanisms

2. Genomics: Single Cell Sequencing

3. Bringing tools together with Big Data: Deep Learning Tools

4. Structural Biology: CryoEM leads small compound design

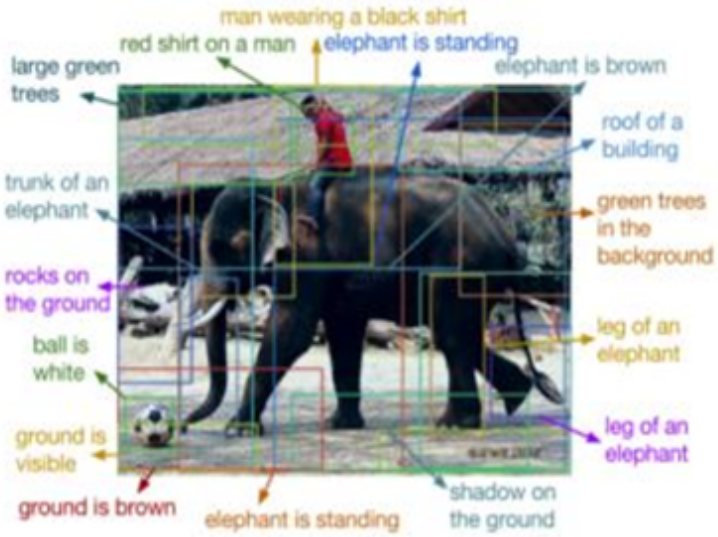
5. Technology meets Application: CRISPR

6. Immune Oncology: Immunotherapy, CAR-T and more …

3. Big Data: Deep Learning Tools or AI

Speech recognition

Computer vision

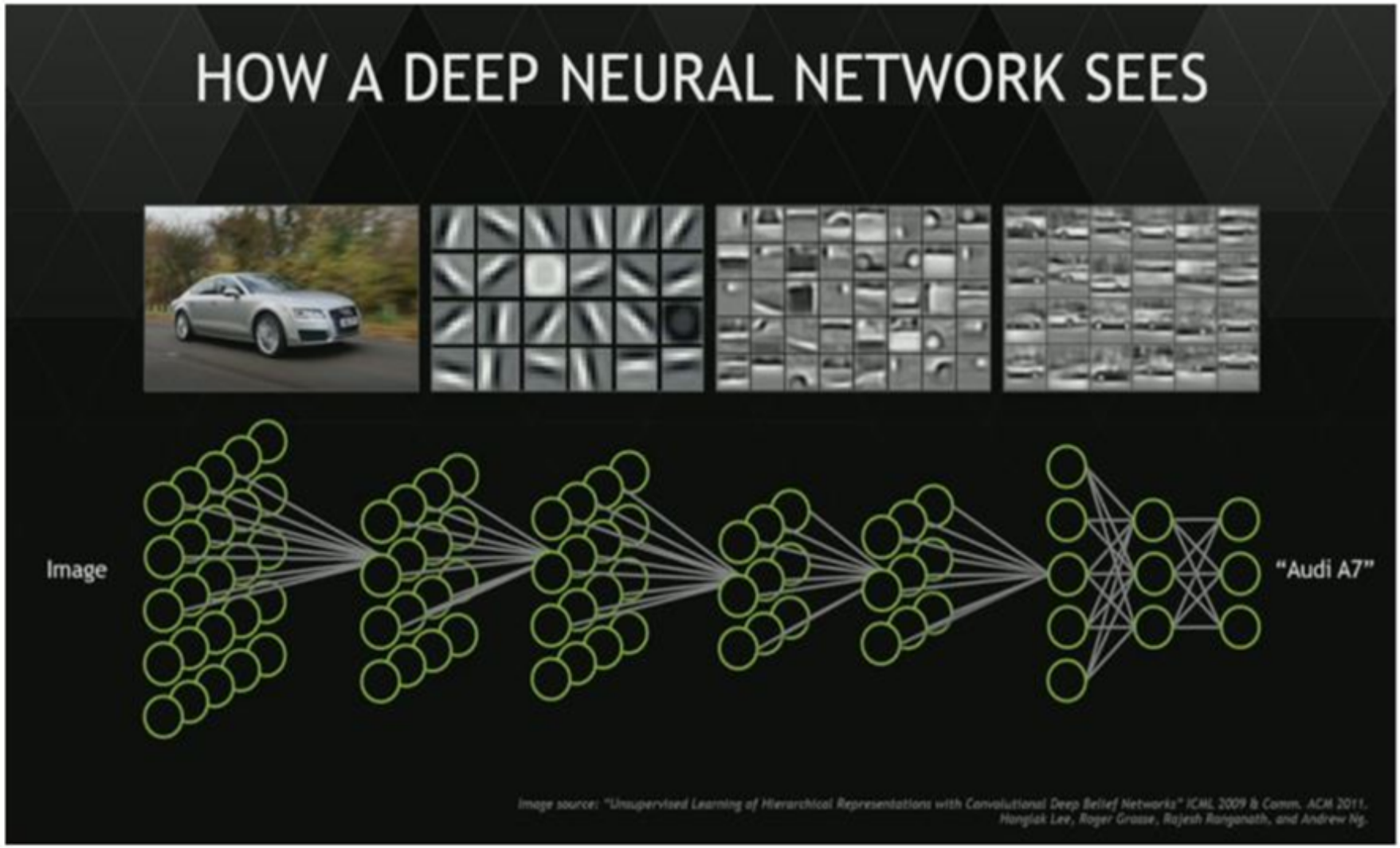


Self-driving cars

Go game

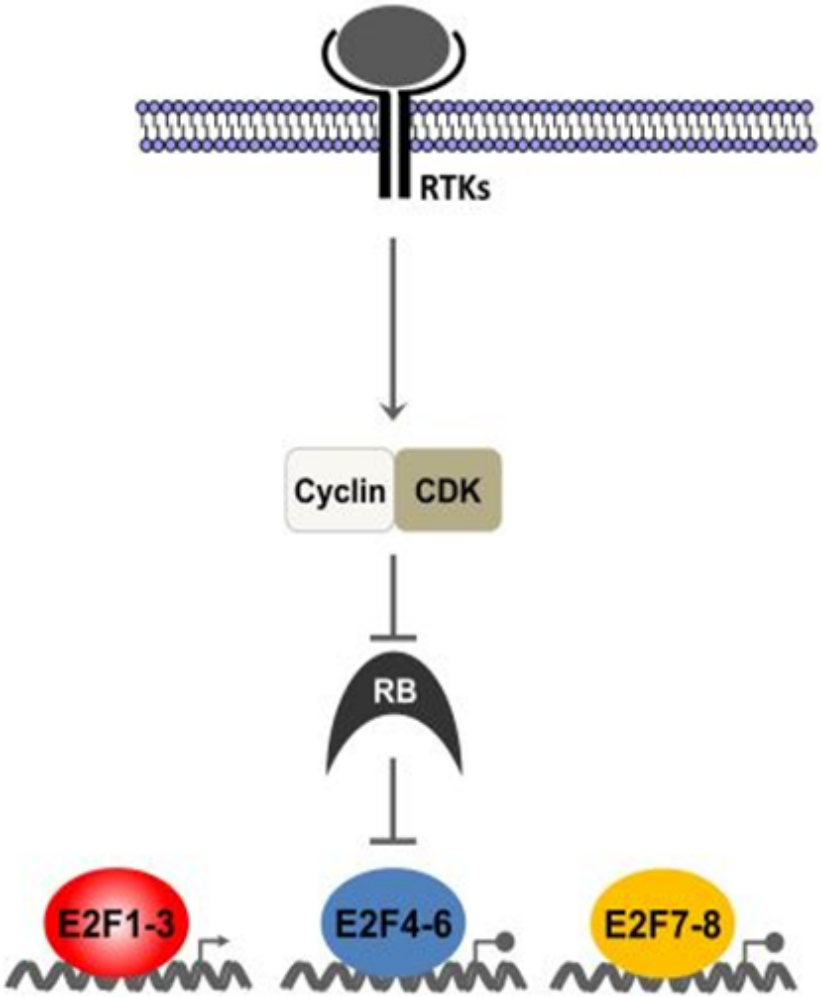
Tech industry

Art



https://mbi.nus.edu.sg/science-features/a-i-in-the-fight-against-cancer/

The RB-E2F pathway in cell cycle control

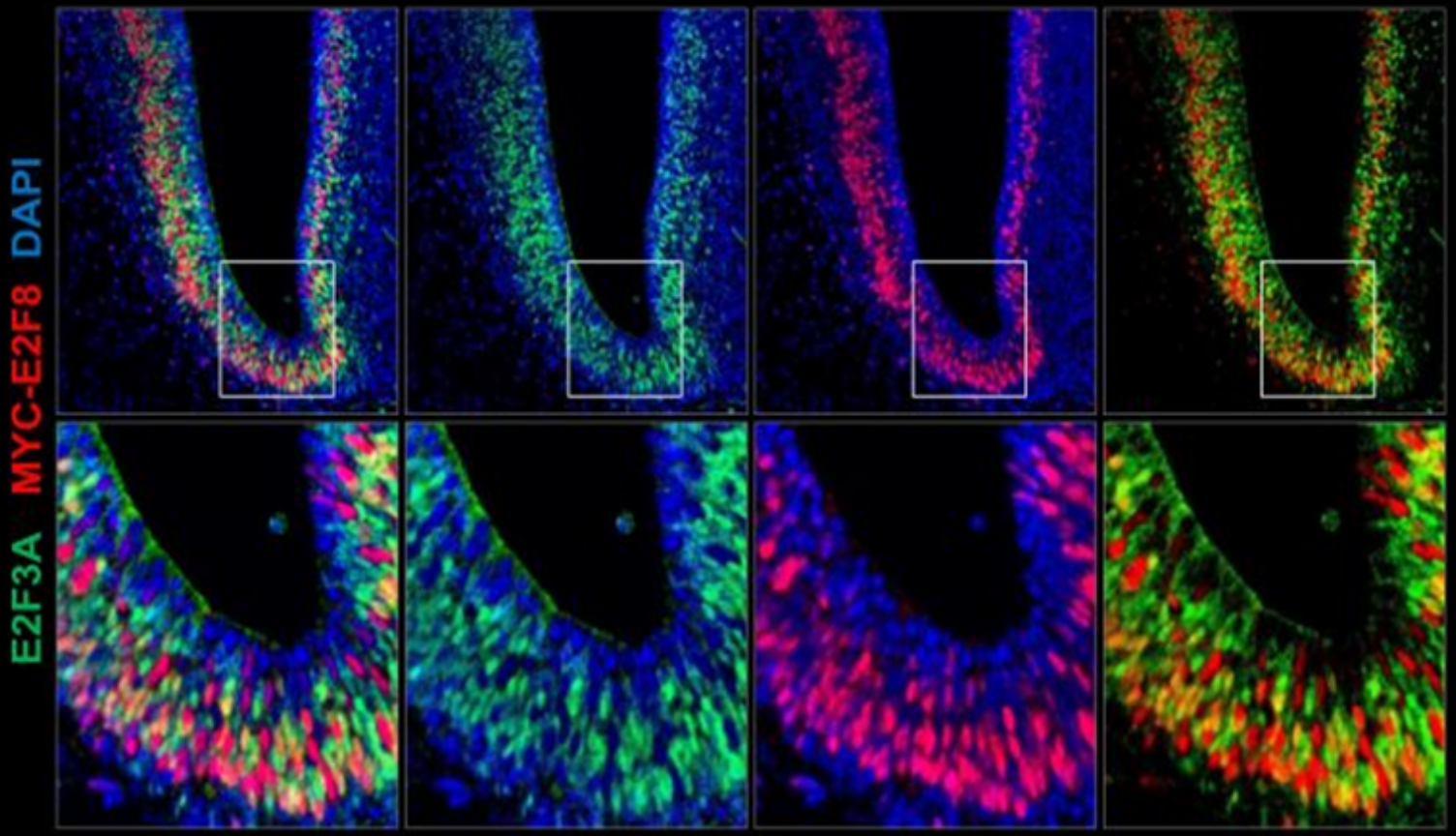


Thierry Pecot, PhD

Cecilia Cuitino
DVM, PhD

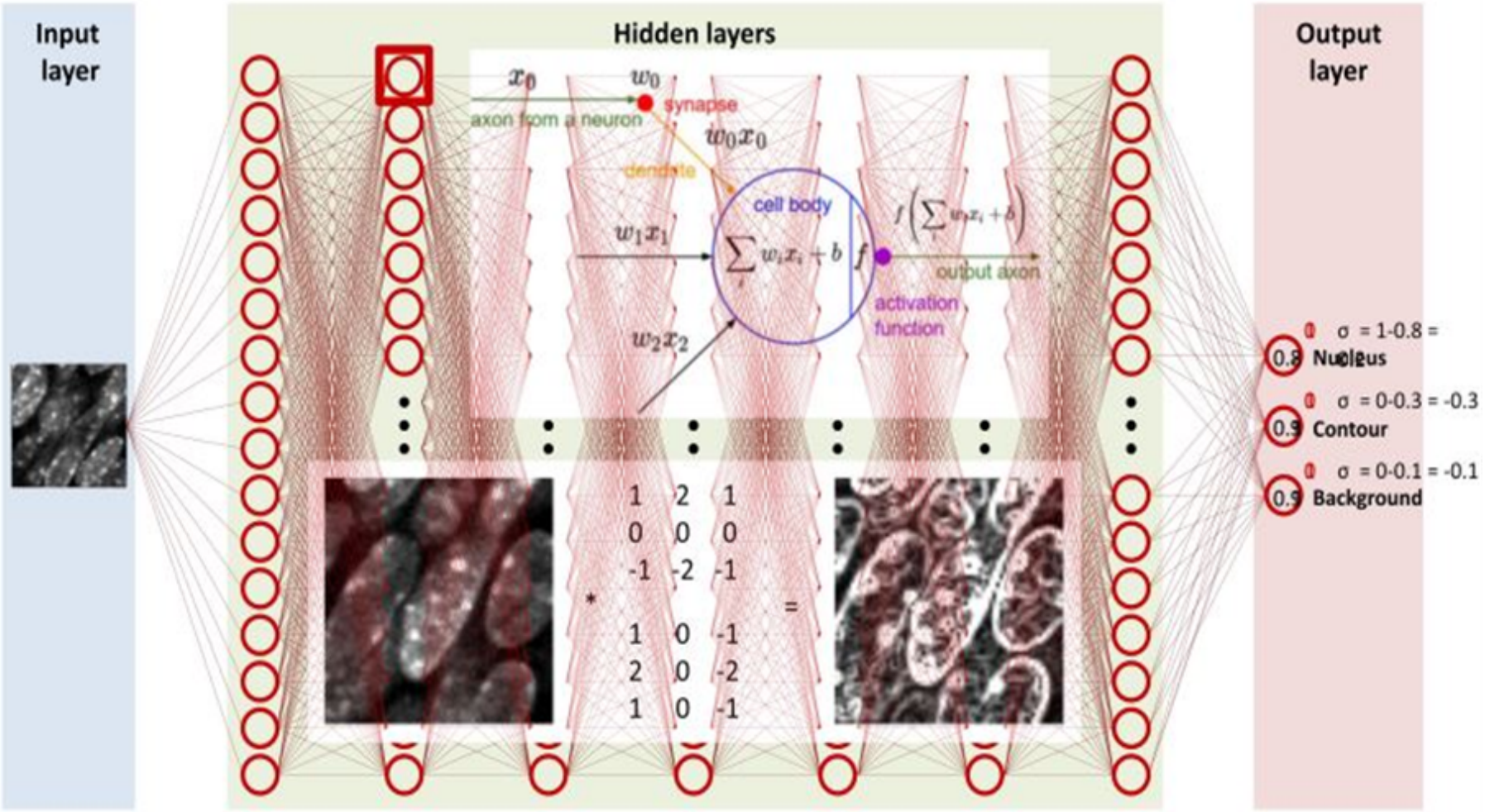
Distinct & overlapping expression of E2F3A & E2F8 & E2F4

Subventricular zone (E13.5)



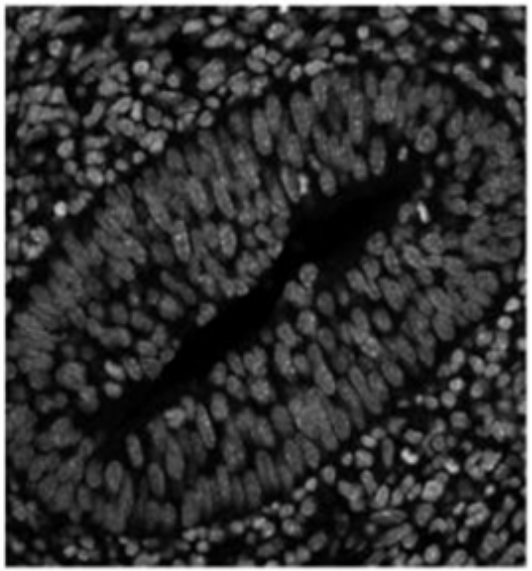
Cuitino et.al., 2019. Dev Cell (in press)

DEEP CONVOLUTIONAL NEURAL NETWORKS

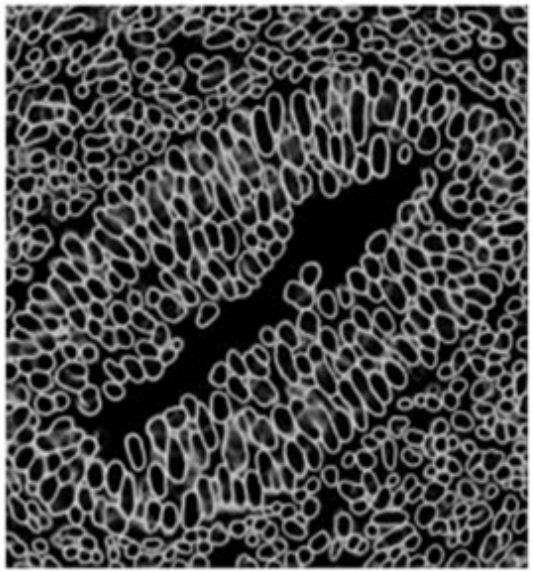


RESULTS: NUCLEI SEGMENTATION

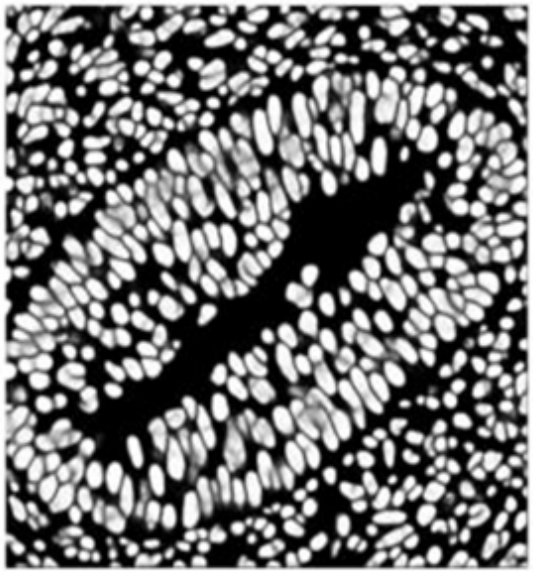
Input DAPI image



Estimated **contour** component

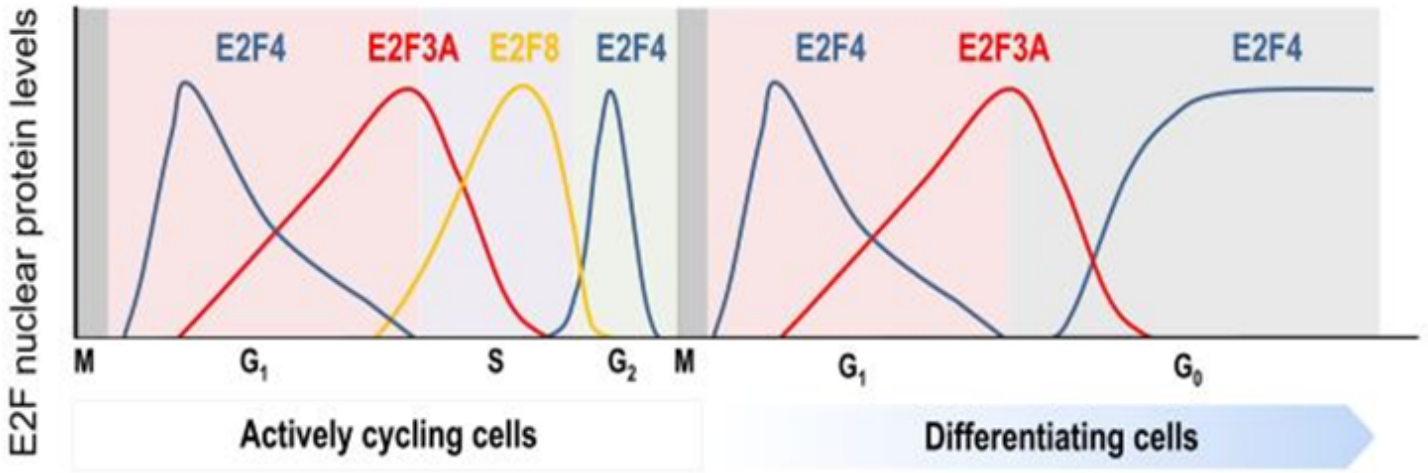


Estimated **nucleus** component



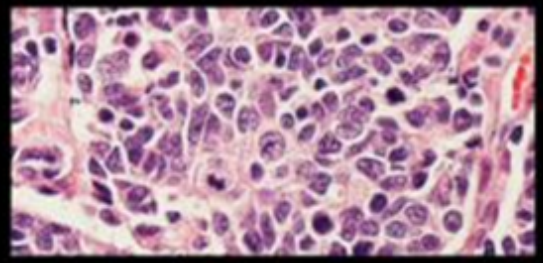
Precision = 0.92
Recall = 0.93

Temporal Nuclear E2F Protein Expression During the Cell Cycle & Differentiation

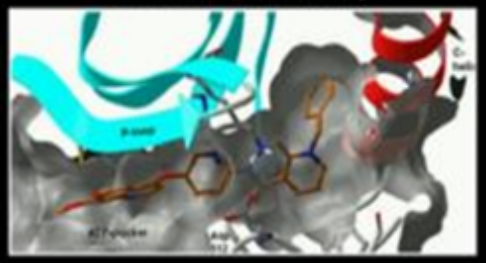


DEEP LEARNING REVOLUTIONIZING MEDICAL RESEARCH

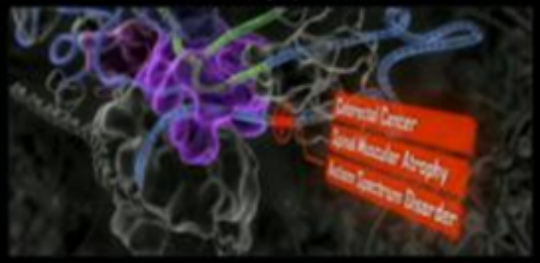
Detecting Mitosis in Breast Cancer Cells
– IDSIA



Predicting the Toxicity of New Drugs
– Johannes Kepler University



Understanding Gene Mutation to Prevent Disease
– University of Toronto



https://mbi.nus.edu.sg/science-features/a-i-in-the-fight-against-cancer/

OUTLINE

1. Model Organisms: discovery and testing cancer mechanisms

2. Genomics: Single Cell Sequencing

3. Bringing tools together with Big Data: Deep Learning Tools

4. Structural Biology: CryoEM leads small compound design

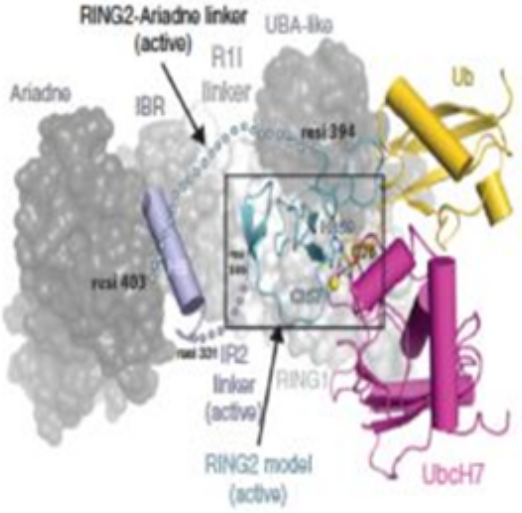
5. Technology meets Application: CRISPR

6. Immune Oncology: Immunotherapy, CAR-T and more …

4. Revolution in structural biology: CryoEM

Paradigm-shifting

Discovery

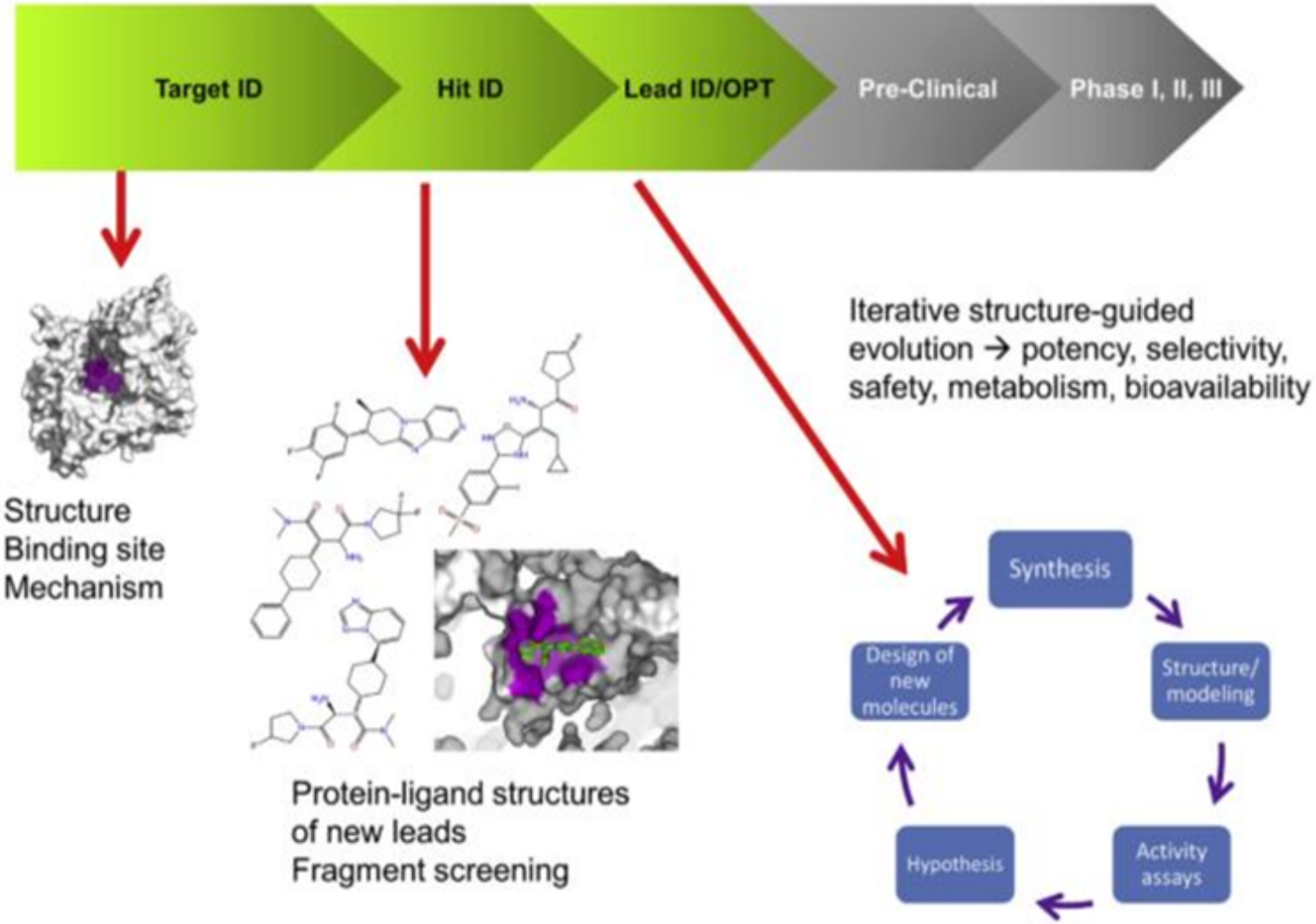


Cell Chemical Biology
Volume 25, Issue 11, 15 November 2018, Pages 1318-1325

Perspective

Cryo-EM for Small Molecules Discovery, Design, Understanding, and Application

Giovanna Scapin [1], Clinton S. Potter [2, 3], Bridget Carragher [2, 3]



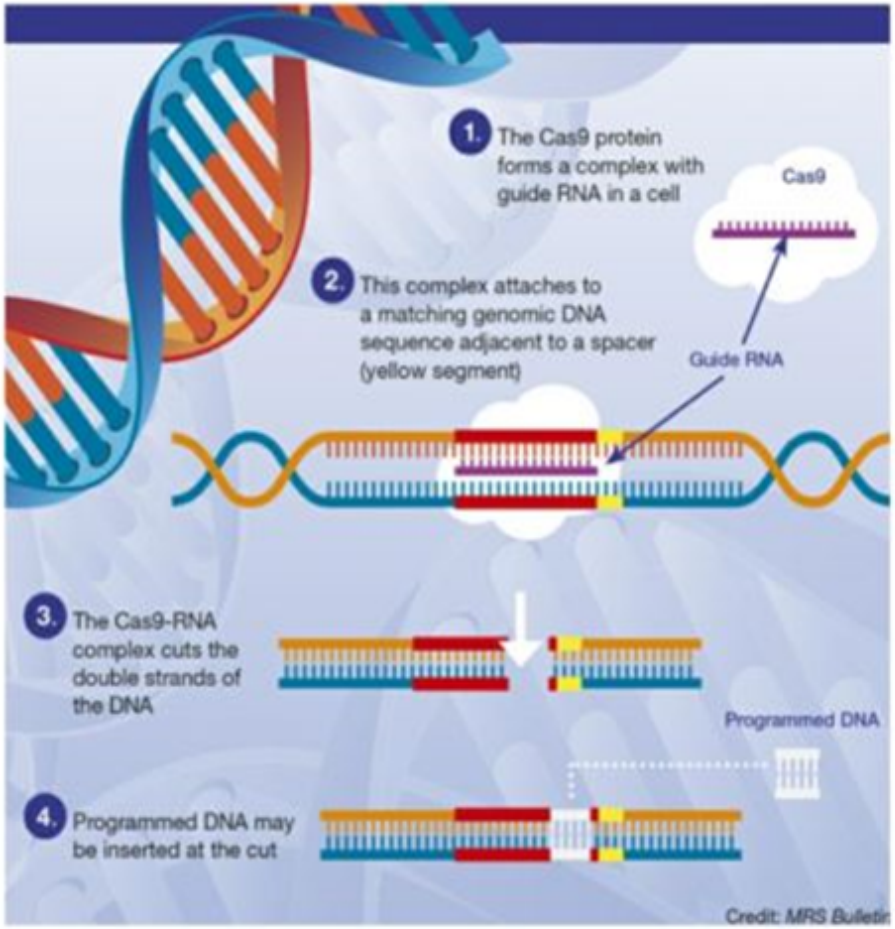
OUTLINE

1. Model Organisms: discovery and testing cancer mechanisms
2. Genomics: Single Cell Sequencing
3. Bringing tools together with Big Data: Deep Learning Tools
4. Structural Biology: CryoEM leads small compound design
5. **Technology meets Application: CRISPR**
6. Immune Oncology: Immunotherapy, CAR-T and more …

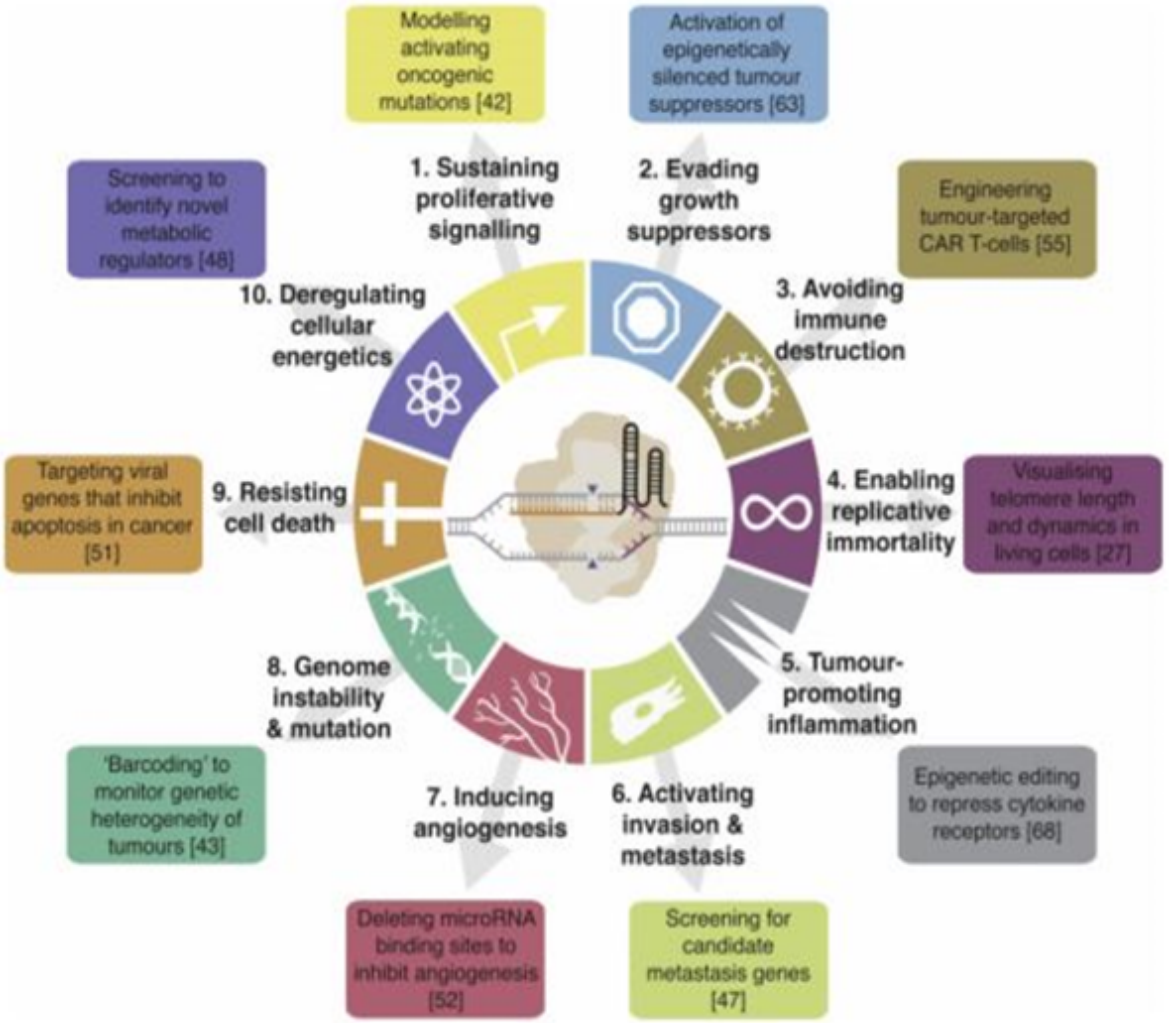
5. CRISPR Technology: from bacteria to cancer therapy

clustered regularly interspaced short palindromic repeats

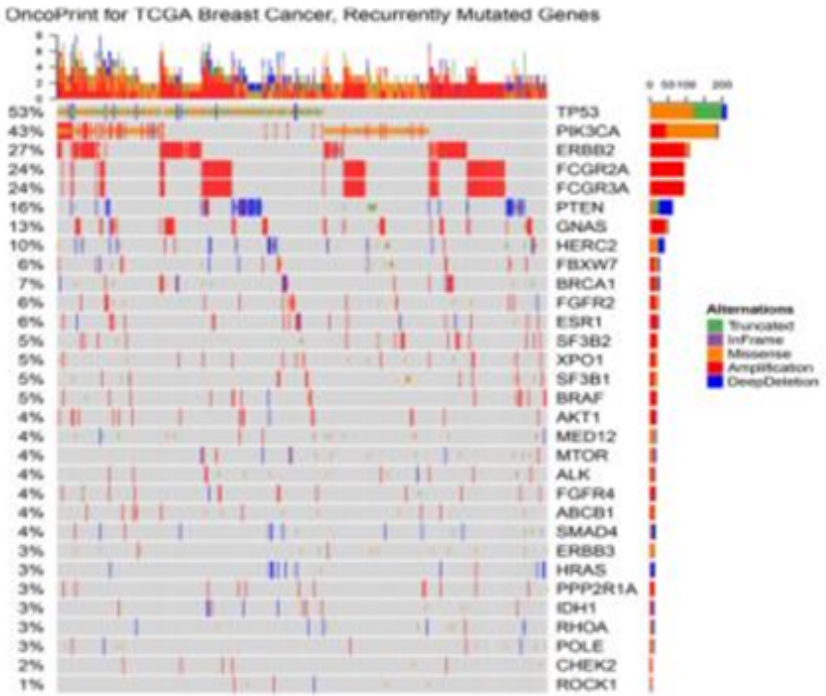
CRISPR Technology: how it works



CRISPR Technology: Targeting cancer

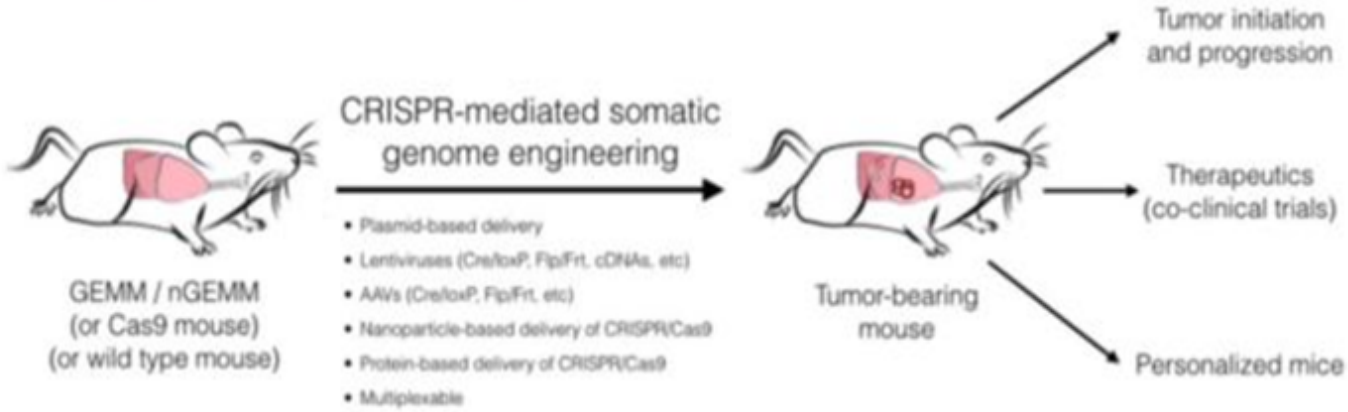


TCGA: Targeting the Lower Frequency Mutated Genes

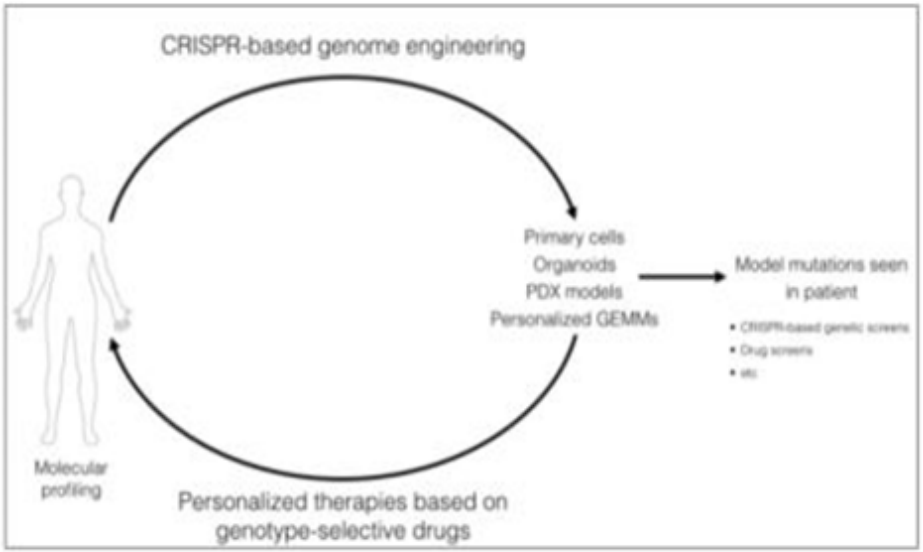


Ding, Wan-Jun & Zeng, Tao & Wang, Li-Jun & Lei, Hong-Bo & Ge, Wei & Wang, Zhi. (2017). **Genes with mutation significance were highly associated with the clinical pattern of patients with breast cancer.**

Oncotarget. 8. 10.18632/oncotarget.21453.



Launching the first Clinical Trial using CRISPR Technology



- First human clinical trial in the U.S. involving the gene-editing tool CRISPR (CAR T): **Phase 1 Trial of Autologous T Cells engineered with CRISPR Technology.**

- The study will enroll up to 18 patients fighting three different types of cancer: **multiple myeloma, sarcoma, and melanoma.**

- To help enhance the treatment, **two genes will be CRISPR deleted in patients' T cells** to make them better cancer fighters: PD-1 and TCR (danger sensing receptor). An engineered receptor, added in its place (NY-ESO-1 TCR), will instead steer them toward particular tumors.

OUTLINE

1. Model Organisms: discovery and testing cancer mechanisms

2. Genomics: Single Cell Sequencing

3. Structural Biology: CryoEM leads small compound design

4. Technology meets Application: CRISPR

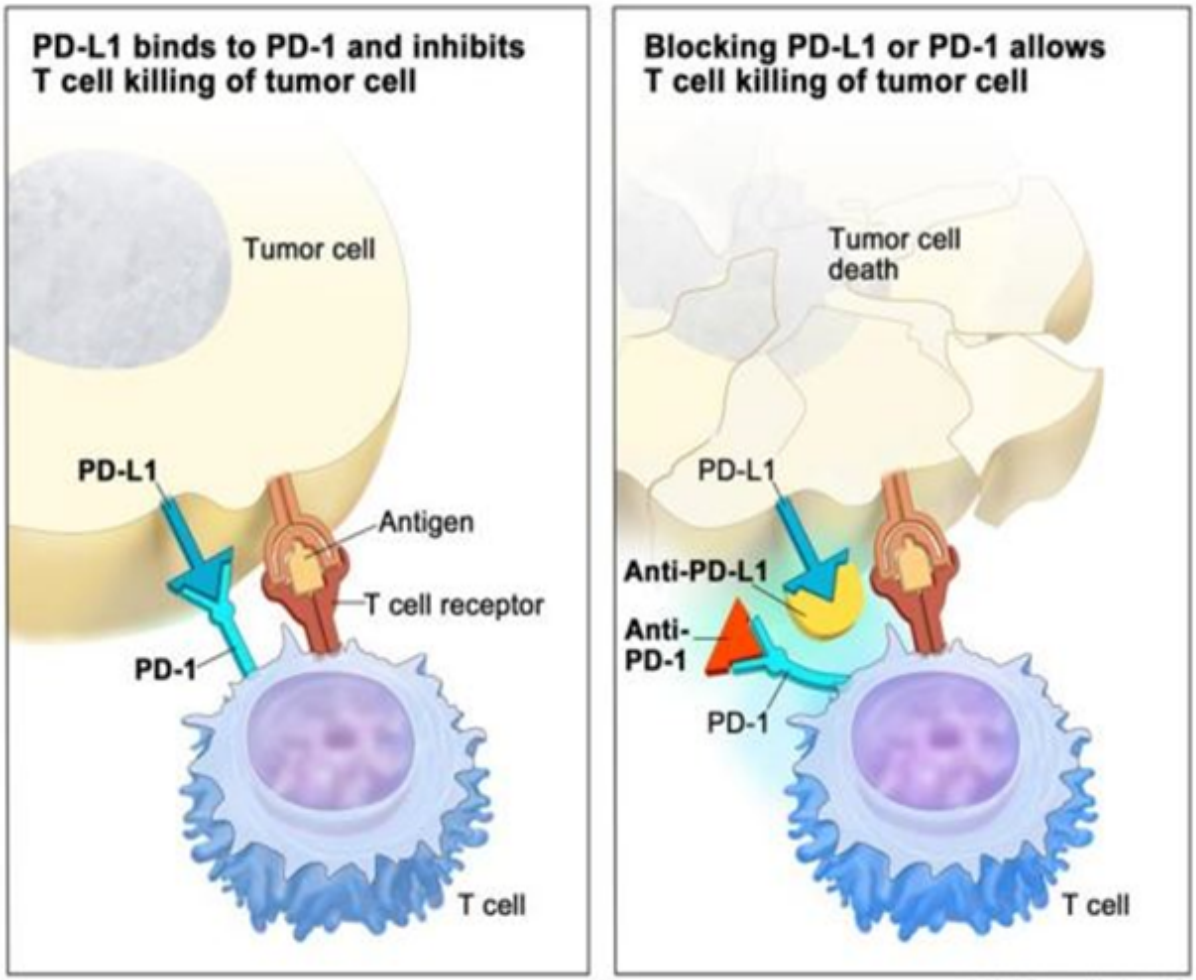
5. Immune Oncology: Immunotherapy, CAR-T and more …

6. Bringing tools together with Big Data: Deep Learning Tools

This past decade will be considered The Dawn of Immunotherapy:

Check point blockade & CAR-T

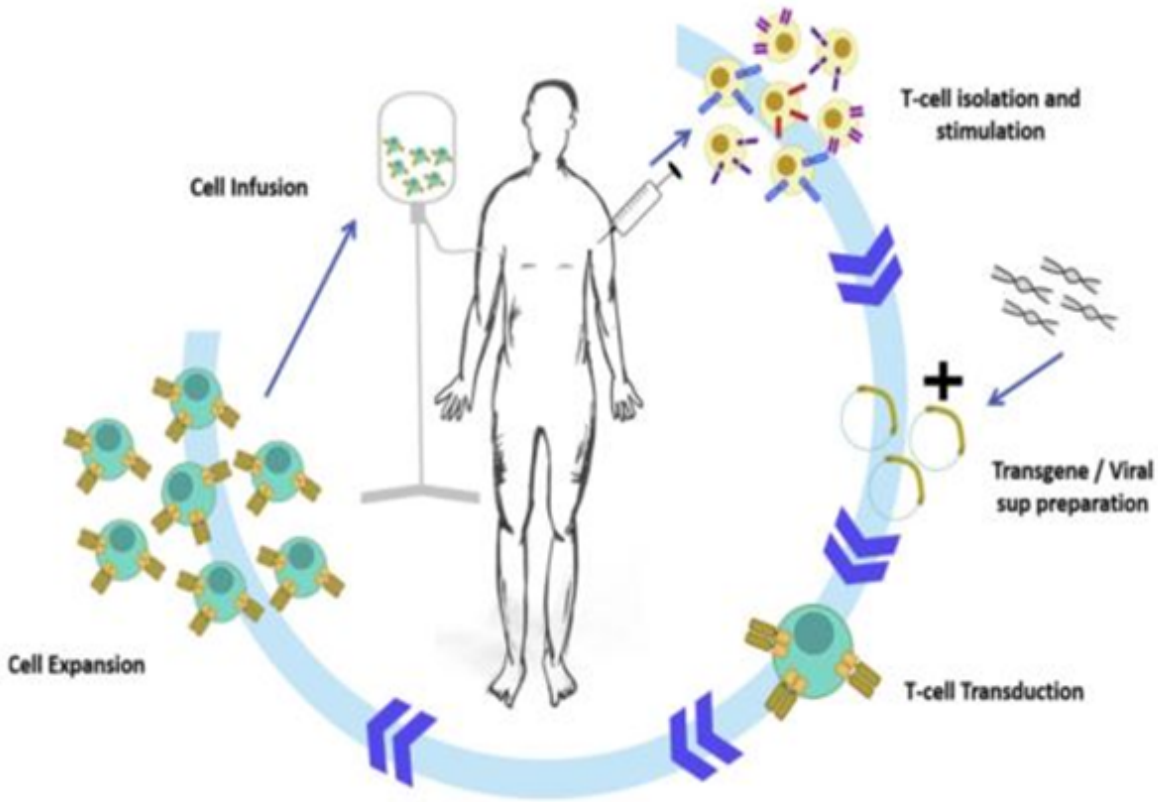
Check point blockade: PD1 or PDL1 Inhibitors



© 2015 Terese Winslow LLC
U.S. Govt. has certain rights

CAR-T therapy takes off …..

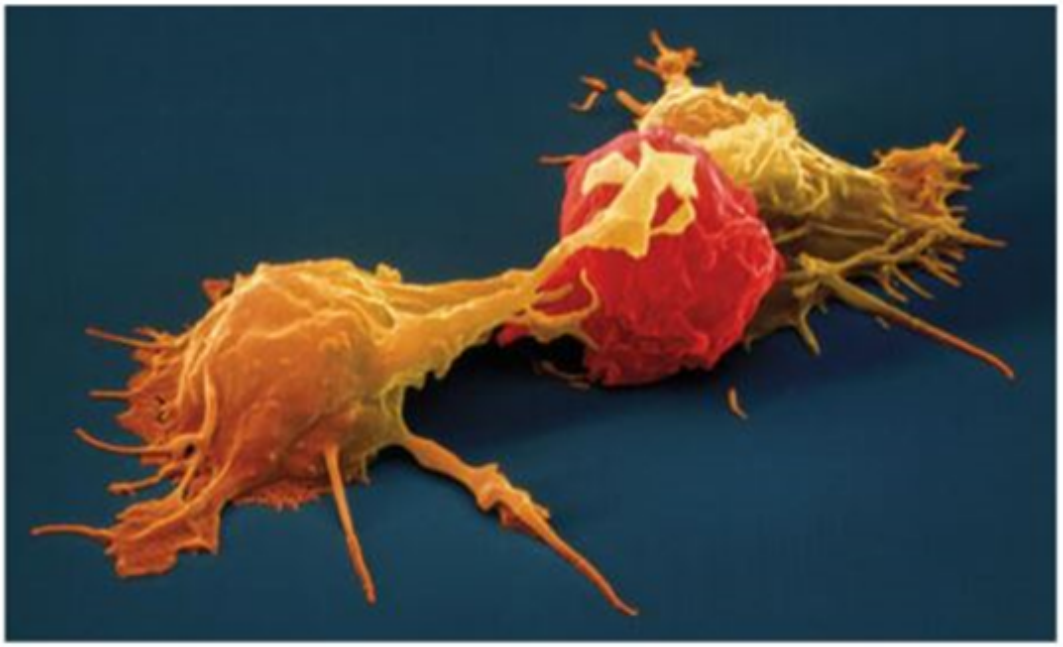
Chimeric Antigen Receptor



- Remissions in 83% of children with previously untreatable acute lymphoblastic leukemia .
- CAR T cells, though, don't work well against solid tumors.

Novel Avenues of Immune Oncology:
NK Cells and Macrophages

Rachidi et.al., 2017.



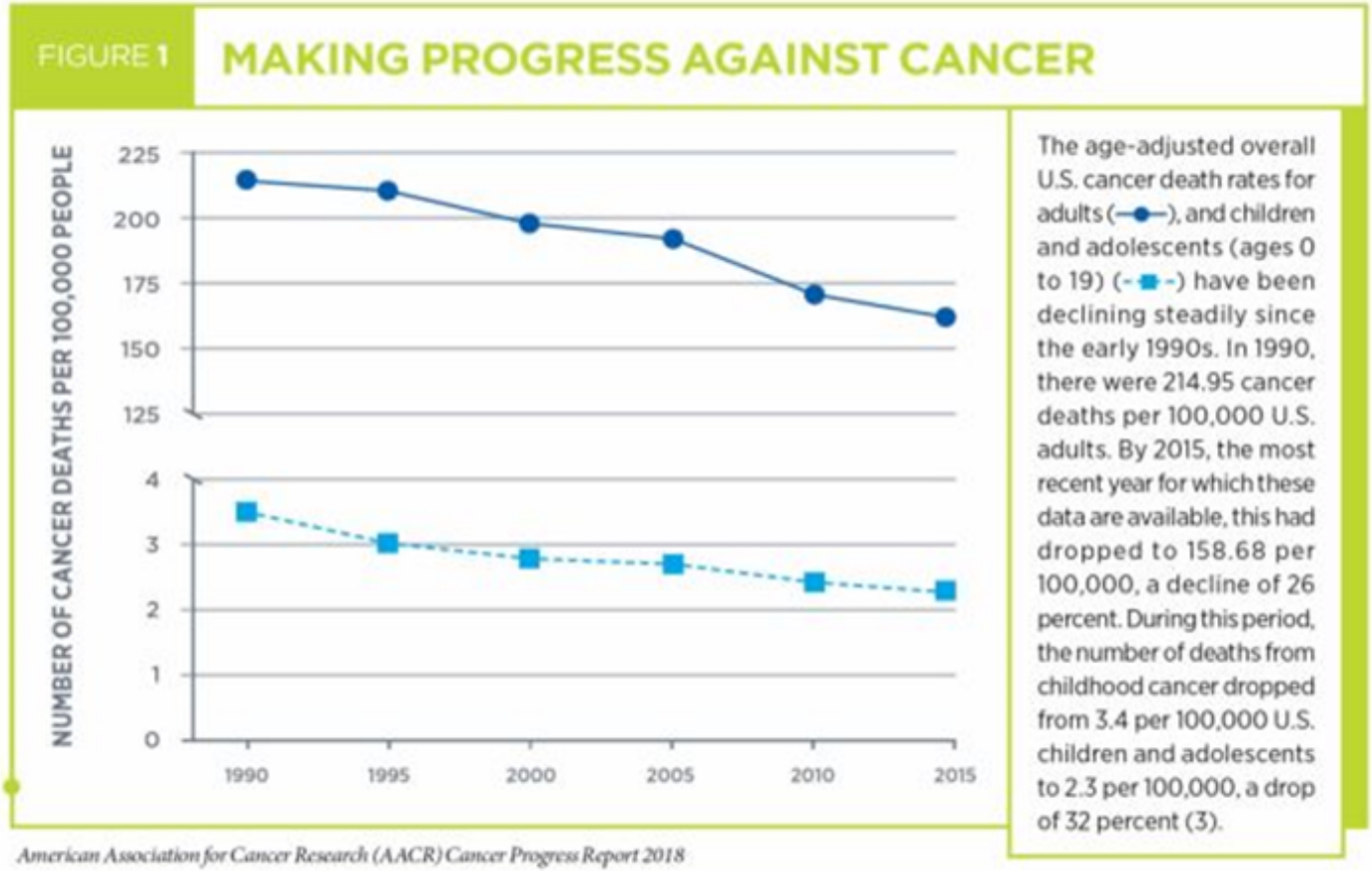
- Natural killer cells equipped with the same type of cancer-homing receptor as CAR T cells make debut in clinical trials for Leukemia (Kati Rezvani, MD Anderson) and glioblastoma.
- CAR natural killer (CAR NK) cells may be safer, faster to produce, and cheaper, and may work in situations where T cells falter.
- CAR macrophages on the horizon of clinical trials (Gill and Klichinsky)

The Human and Financial Economics of Cancer

(710)

American Association for Cancer Research (AACR) Cancer Progress Report 2018

- The costs of cancer care alone stand in stark contrast to the amount of money the federal government invests across all areas of biomedical research.
- In 2015, the same year that the direct medical costs of cancer care were $80.2B, the NCI budget was just $4.93B and total NIH Budget was ~$34B.



- The age-adjusted overall US cancer death rate has been decreasing since the 1990s, translating into almost **2.4 million cancer deaths avoided** between 1990-2015.

- Not all segments of the U.S. population have benefited equally from advances against cancer.

Leone Lab:

Lindsey Kent, PhD
Cecilia Cuitino, PhD DVM
Daokun Sun
Raleigh Kladney
Thierry Pecot, PhD
Taka Uchida PhD
Melodie Parrish
Anthony Trimboli, PhD

Collaborators:

- **Michele Pagano** (NYU)
- **Vincenzo Coppola**

Supported by NIH/NCI, DoD, MoD, PEW Charitable Fund and the LLSociety