

# Blood Cell Development and Cancer

- **Program goal:**

- use genetics to identify genes essential for blood cell development and assess their role in cancer

## Membership

### Basic Science

- Campbell
- Hardy
- Hayakawa
- Kappes
- Rhodes
- Sigal
- Wiest

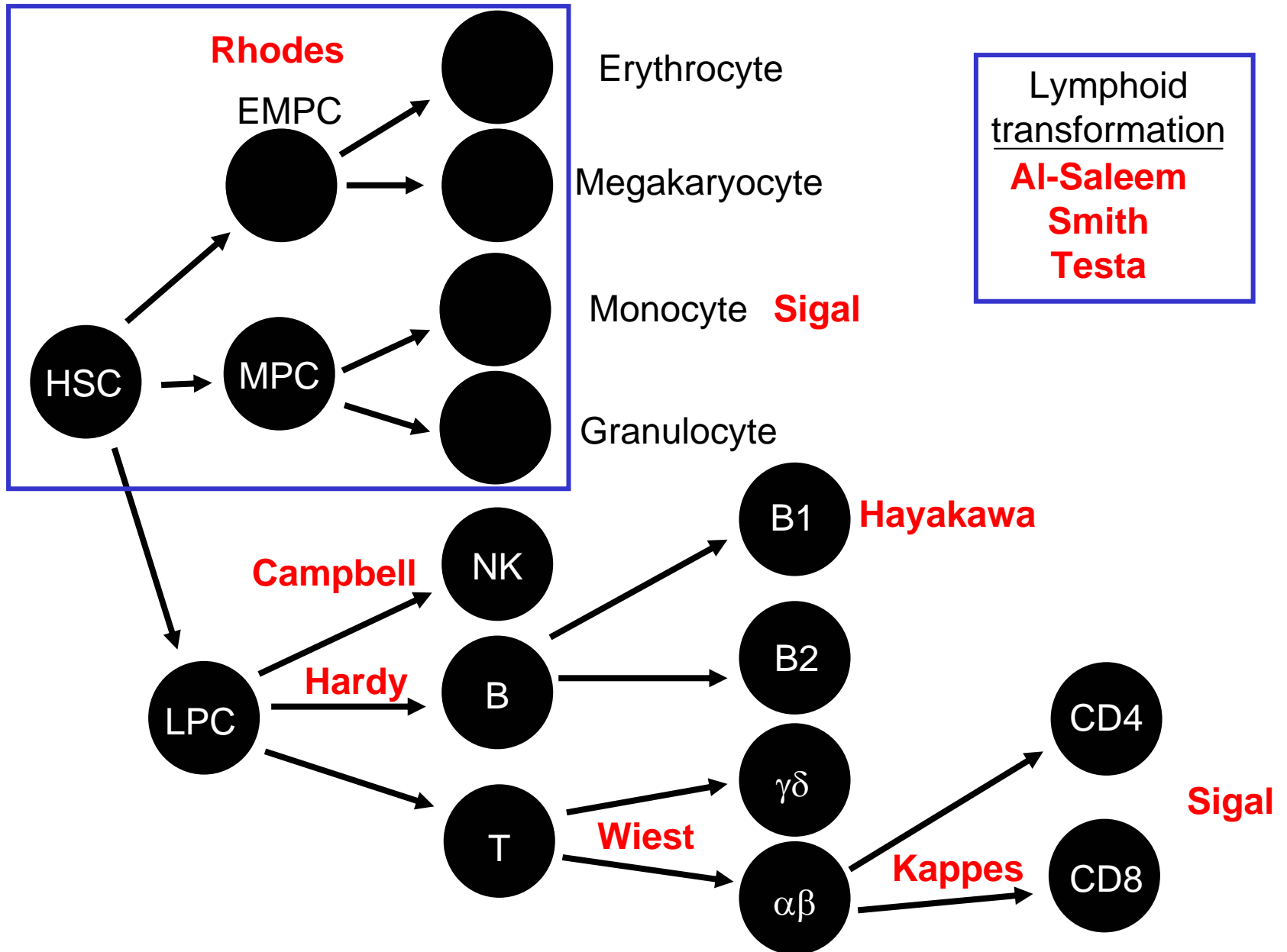
### Bridge

- Testa

### Clinical

- Al Saleem
- Smith

# Blood Cell Development and Cancer

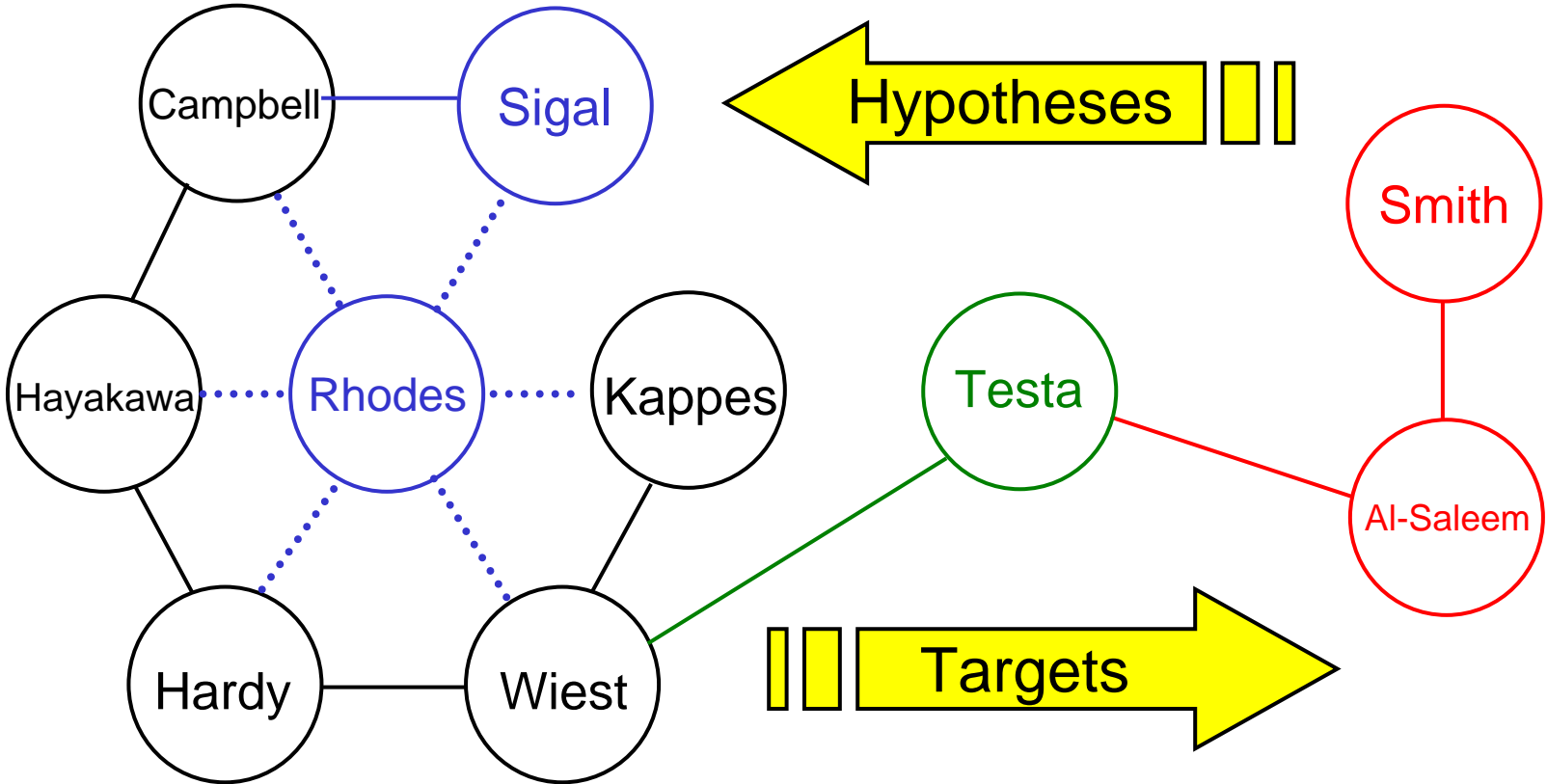


# Blood Cell Development and Cancer

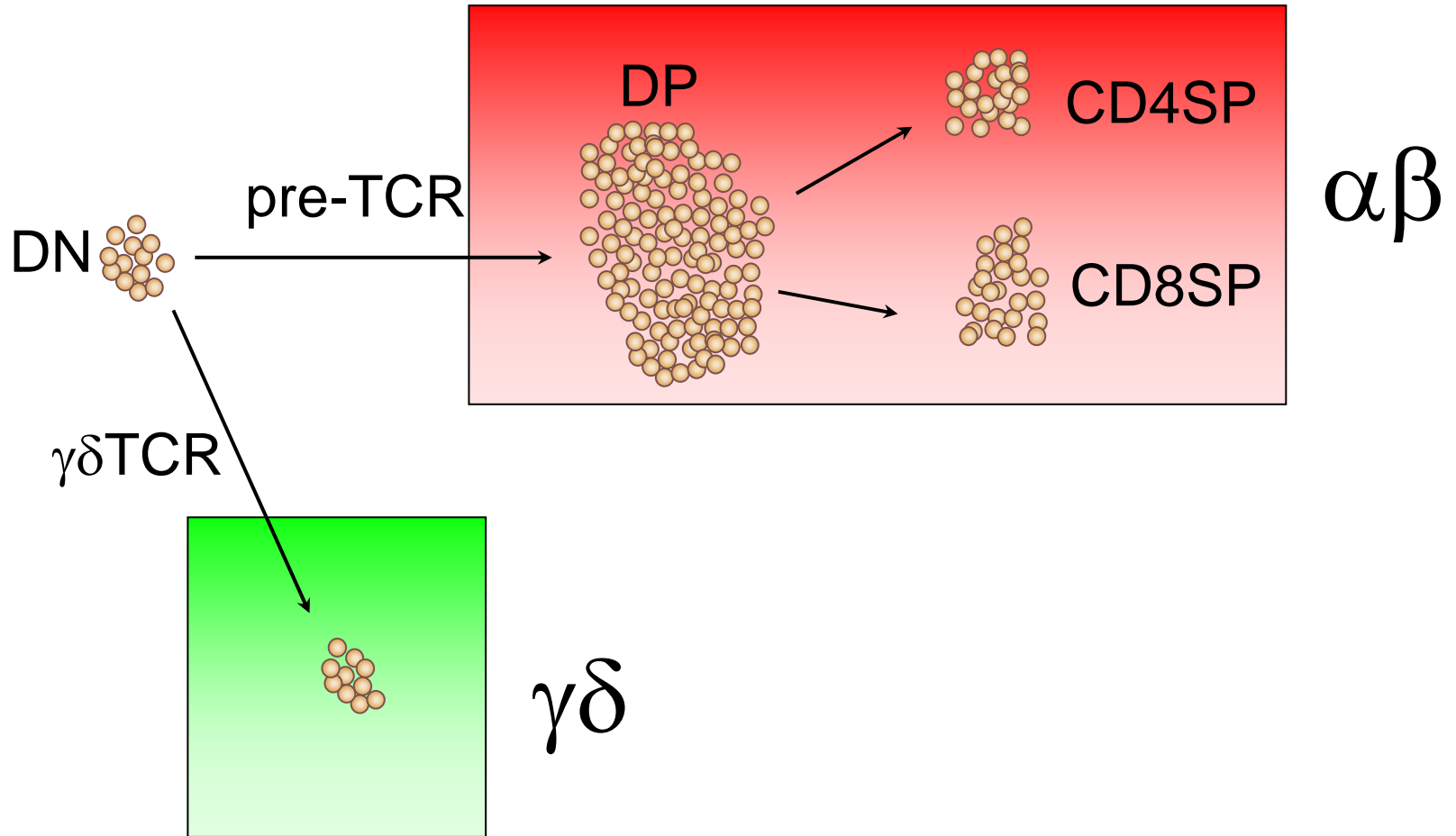
BASIC

BRIDGE

CLINICAL

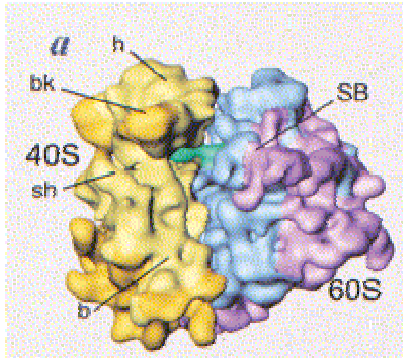


# Thymocyte development



# Directed genetic screen reveals the importance of Rpl22 in T cell development

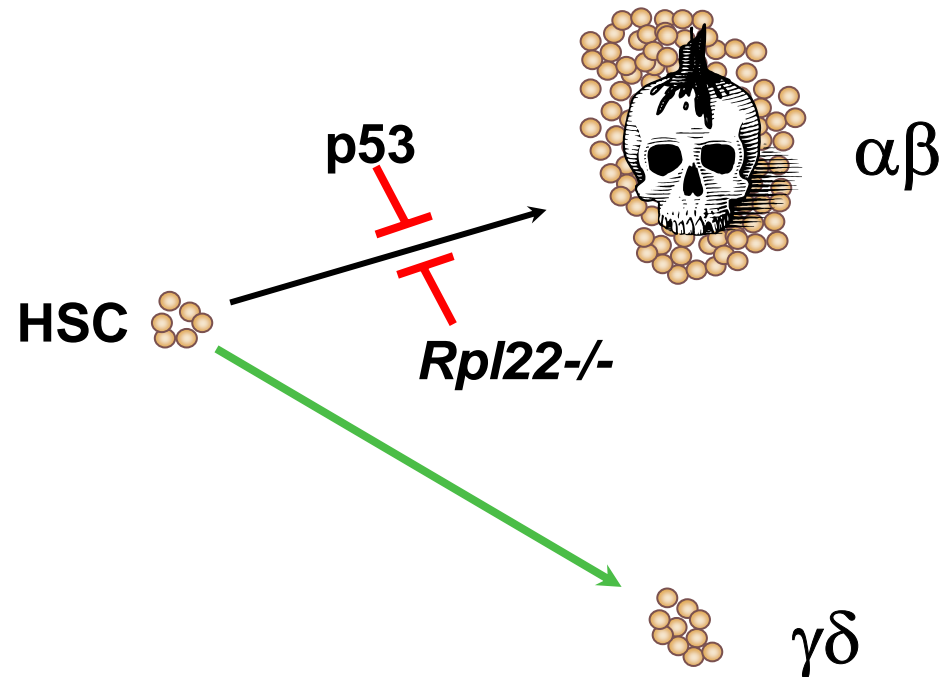
## 80S ribosome



## Rpl22-deficiency selectively blocks $\alpha\beta$ T cell development

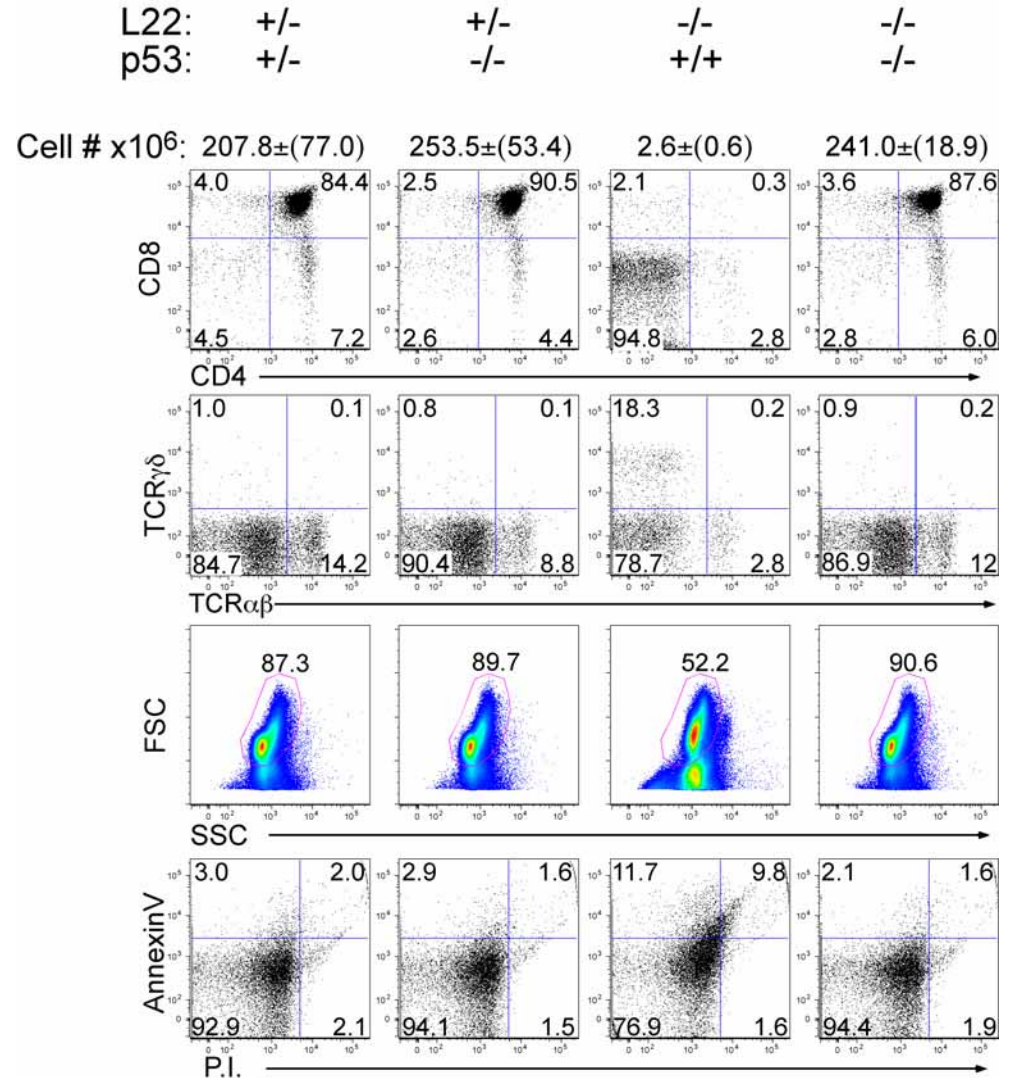
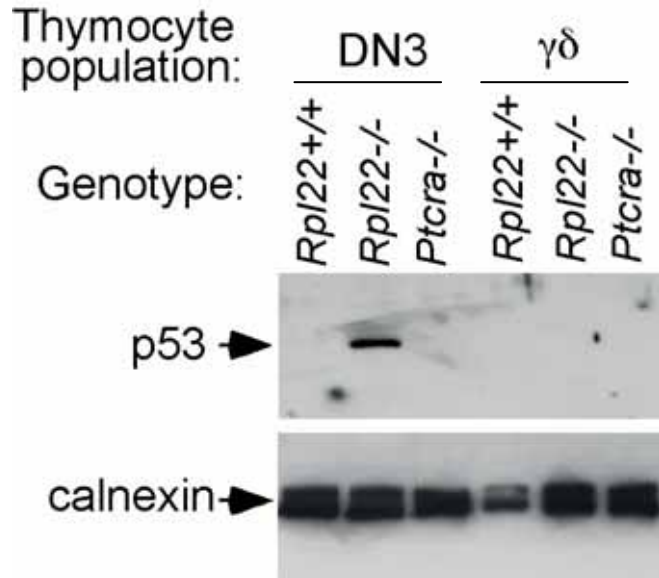
### Rpl22:

- ubiquitously expressed component of the large subunit
- conserved in eukaryotes
- not essential for translation
- function unknown



*Anderson et al., Immunity, 2007*  
*In collaboration with Lexicon Pharmaceuticals*

# Rpl22-deficiency blocks development by selective induction of p53 in $\alpha\beta$ lineage progenitors

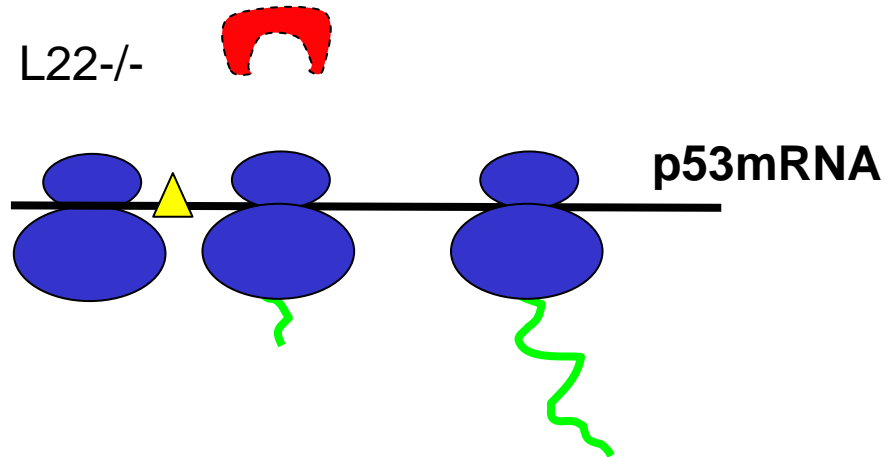
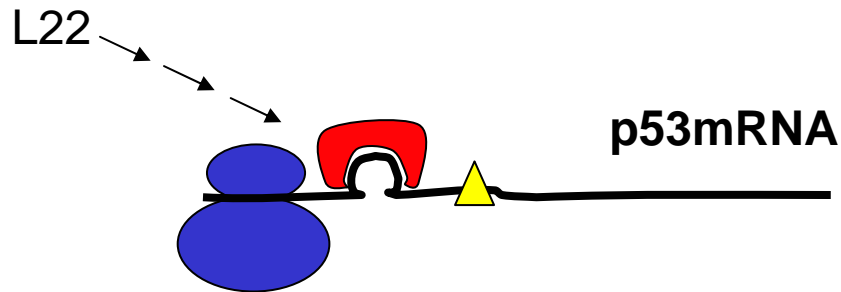


# Potential mechanisms for induction of p53 synthesis

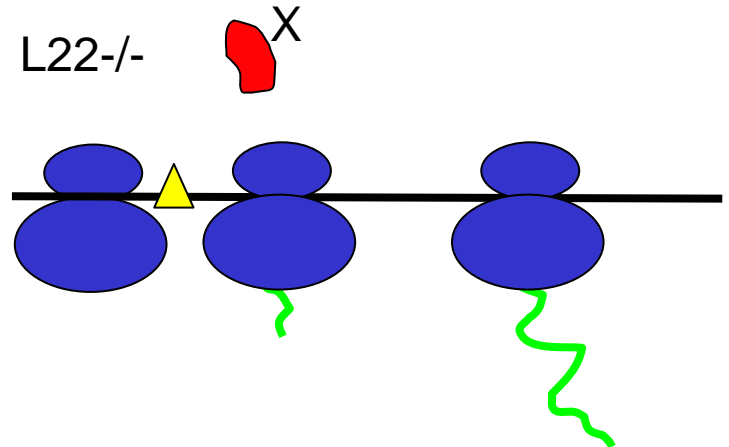
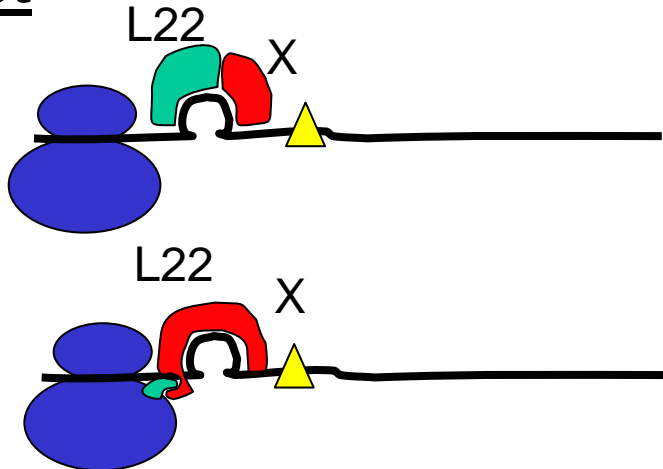
**L22+**

**L22-**

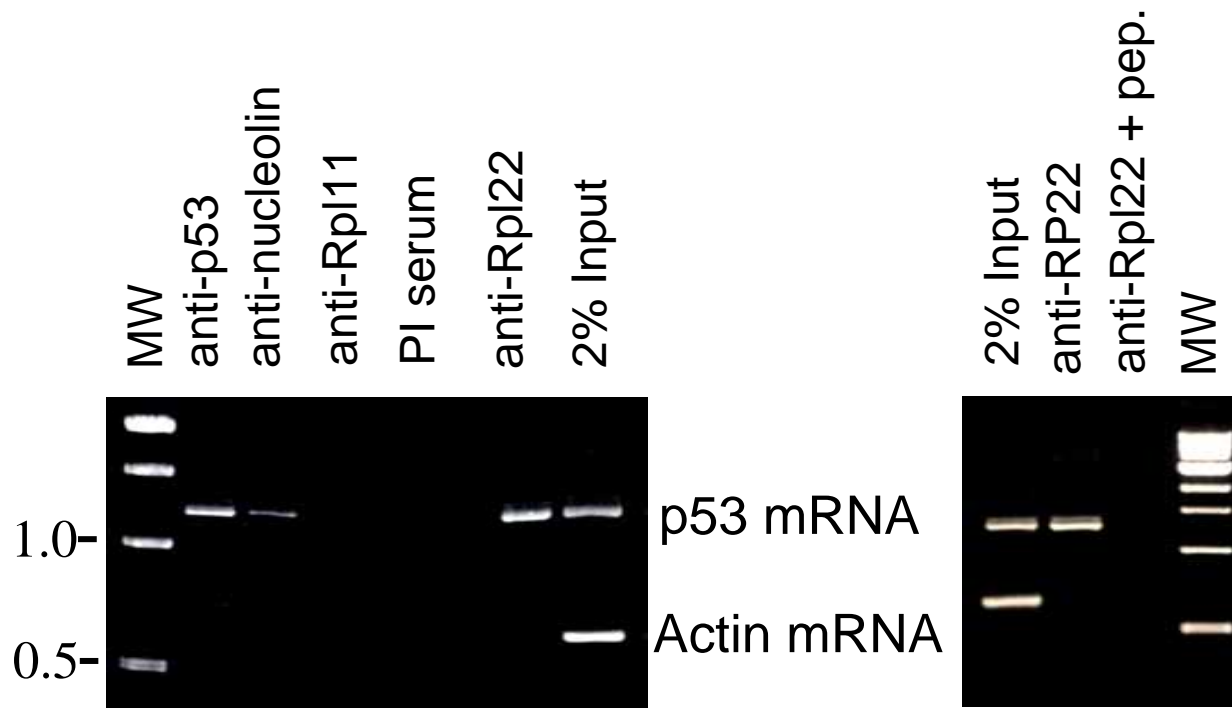
**Indirect**



**Direct**



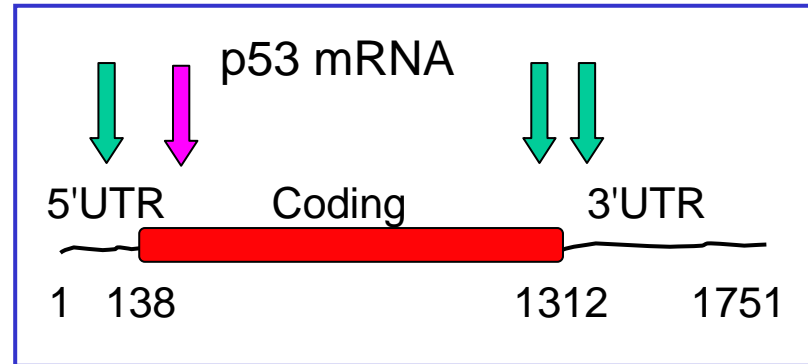
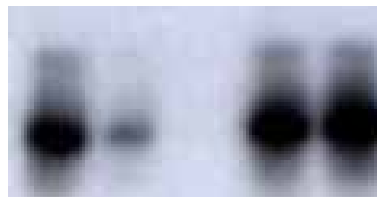
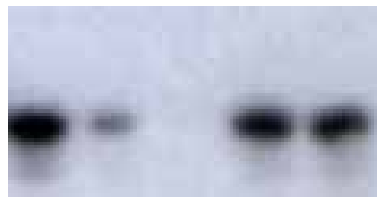
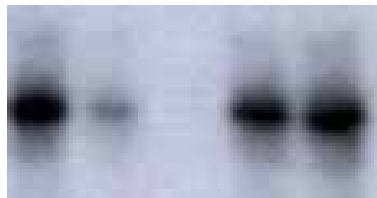
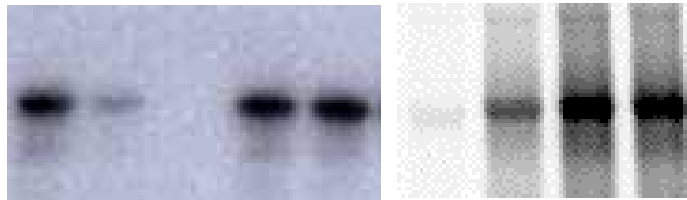
# Anti-Rpl22 Ab pulldown of p53 mRNA



# Effect of Rpl22 on translation of p53 mRNA *in vitro*

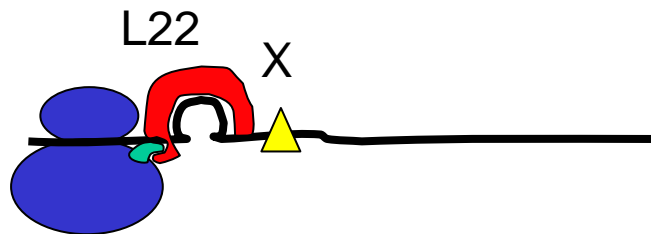
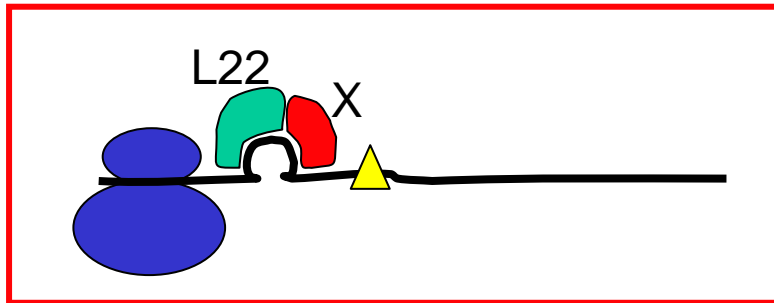
## *In vitro* translation

GST-fusion:	Rpl22			(-)	Rpl22			Rpl11
Boiling:	-	-	-	+	-	-	-	-
pMol:	0	4	10	10	10	4	0	10



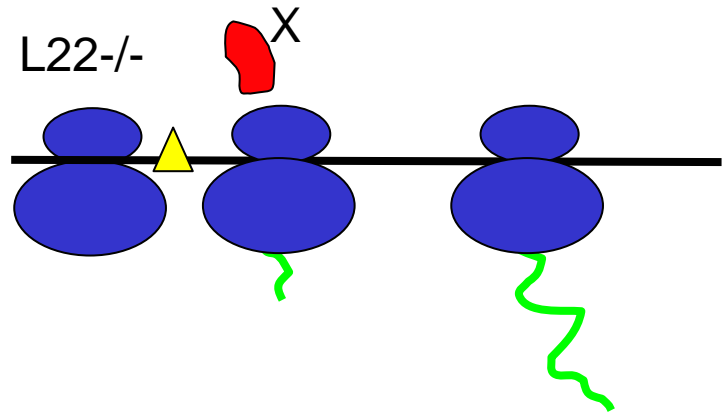
# Potential mechanisms for induction of p53 synthesis

L22+

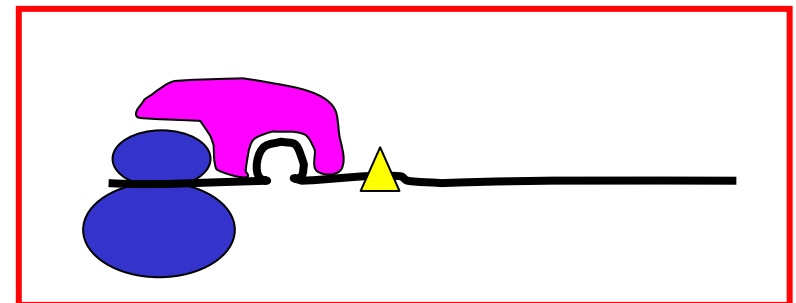


L22-

$\alpha\beta$  lineage precursors



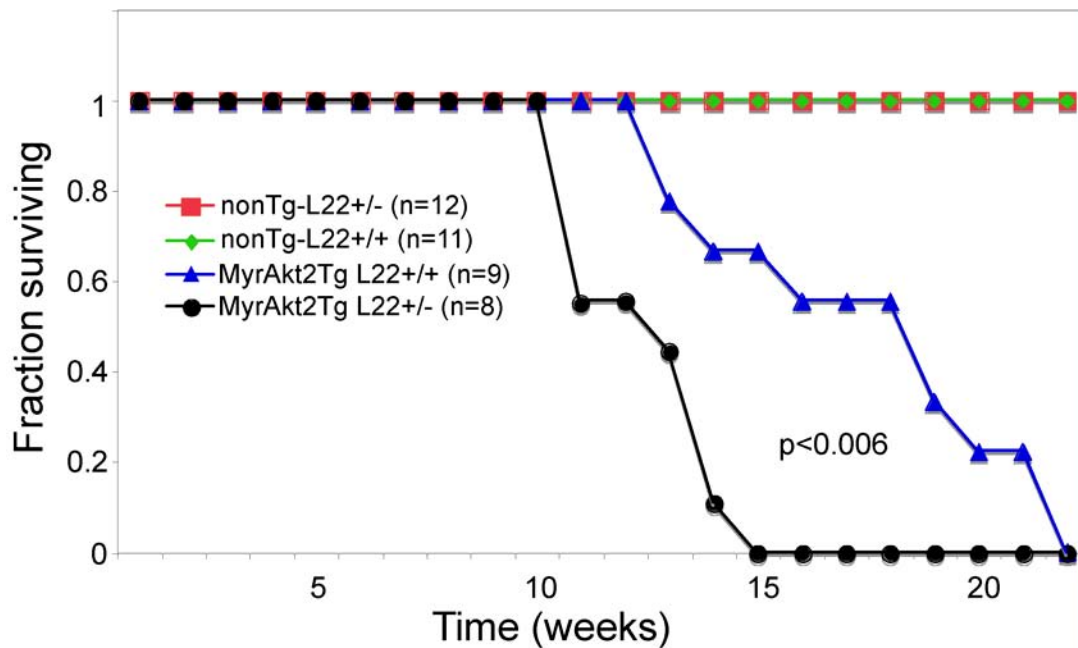
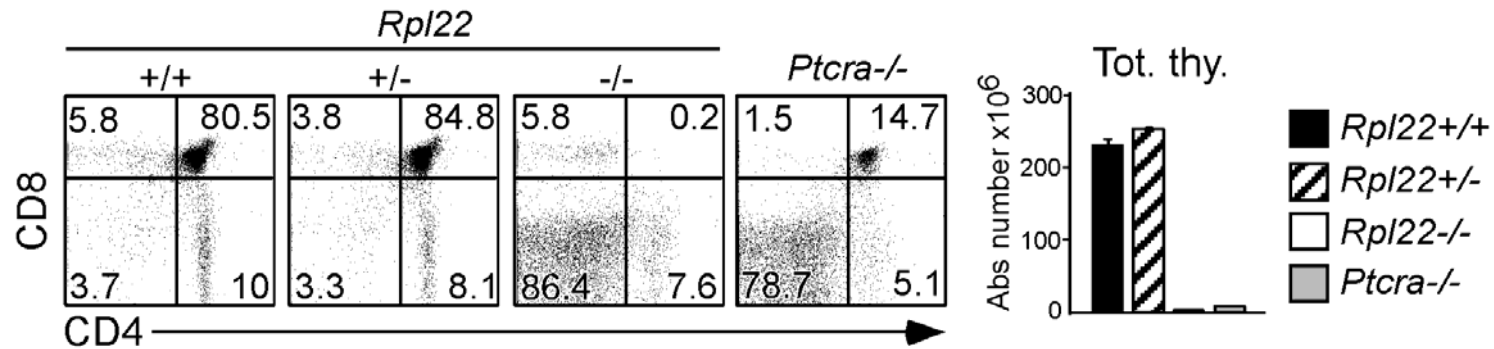
Other cell lineages



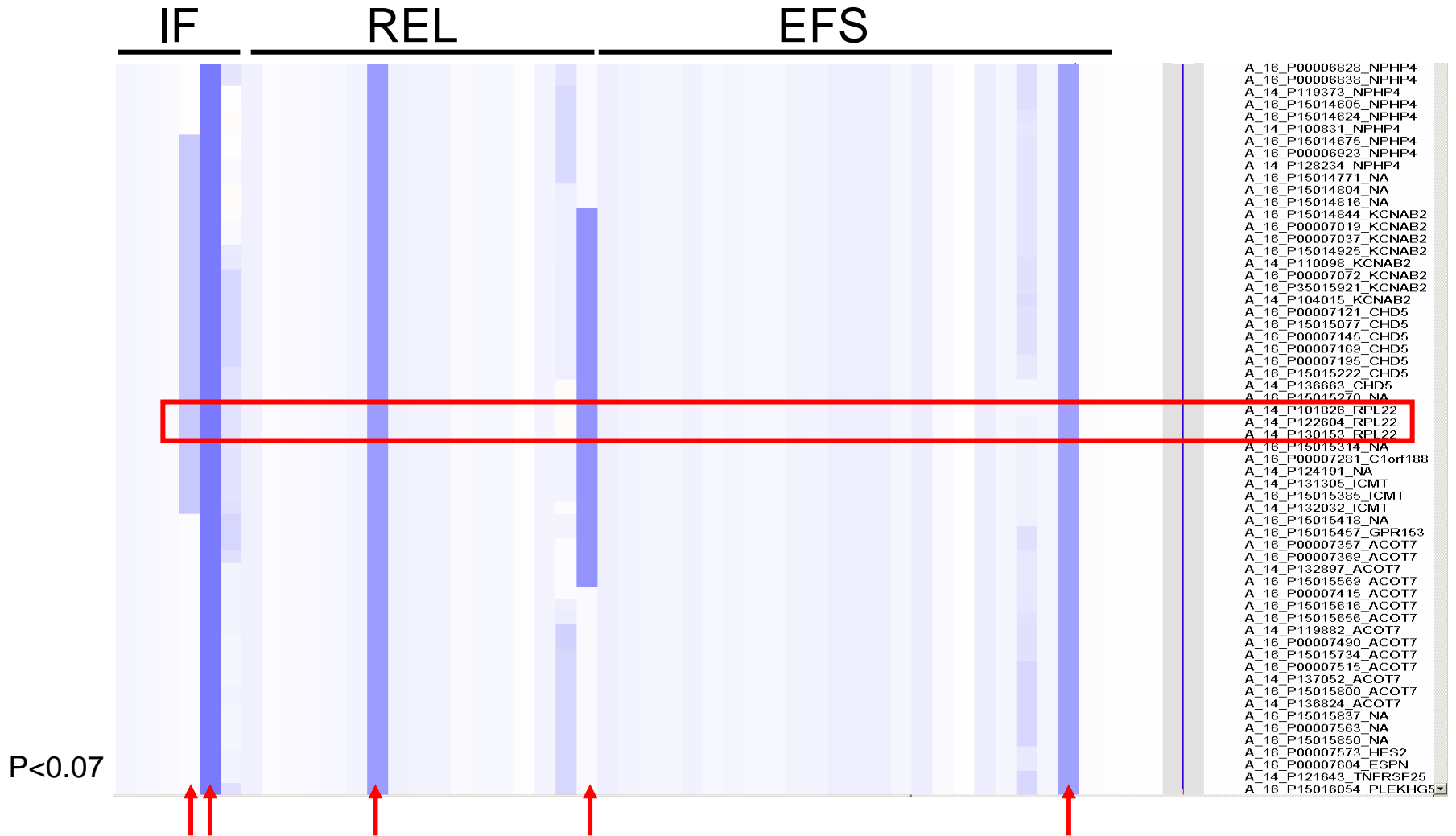
# Rpl22 and T lymphoma

- Ribosomal protein genes are cancer genes in zebrafish
- Rpl22-deficiency specifically blocks T cell development
- Does Rpl22 affect development of thymic lymphomas?
  - Acute lymphoblastic leukemia (ALL) is the most common childhood leukemia - 4000 new cases/yr
  - T-ALL represents a transformed counterpart of early thymocytes
  - T-ALL is frequently associated with mutations activating Notch or Akt

# Loss of one *Rpl22* allele increases thymic cellularity and accelerates development of thymic lymphoma.



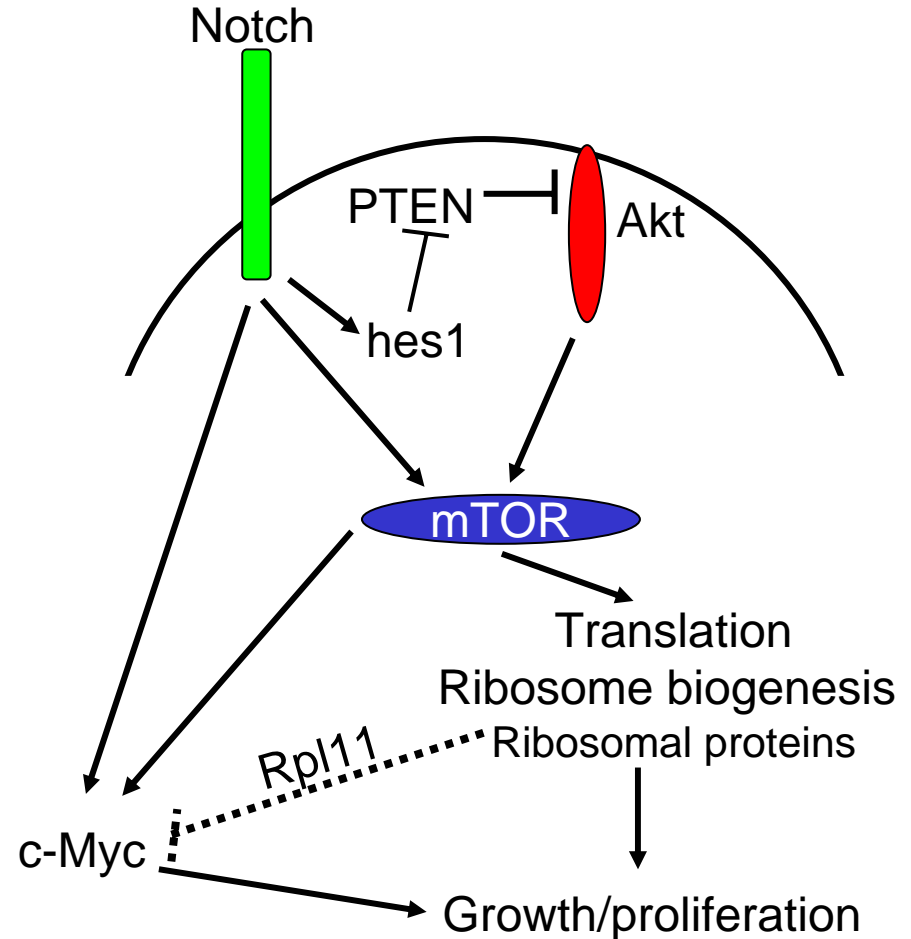
# aCGH analysis of the Rpl22 locus in T-ALL



# Rpl22 and T-ALL

## Loss of one allele of *Rpl22*:

- Causes a slight increase in thymus size
- Accelerates development of murine thymic lymphoma
- Occurs in about 10% of primary T-ALL cases
- Is inversely correlated with survival
- Single inactivating point mutations are found in 1/3 of T-ALL cell lines derived from relapsed T-ALL patients
- Involved in other diseases where 1p36.3-1p36.2 is lost?



# Acknowledgements



## Wiest lab:

Matt Hartman  
J.P. Lauritsen  
Sang-Yun Lee  
Juliette Lefebvre  
Michele Rhodes  
Zhiqiang Zhang

## FCCC:

Maureen Murphy  
Joe Testa

## DFCI:

Tom Look  
Alejandro Gutierrez

## Lexicon Pharm., Inc.

Steve Anderson  
Tamas Oravec