

# Pharmacogenomics in Pediatric Hemato-Oncology



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Recherche du  
CHU Sainte-Justine

*Le centre hospitalier  
universitaire mère-enfant*

*Pour l'amour des enfants*

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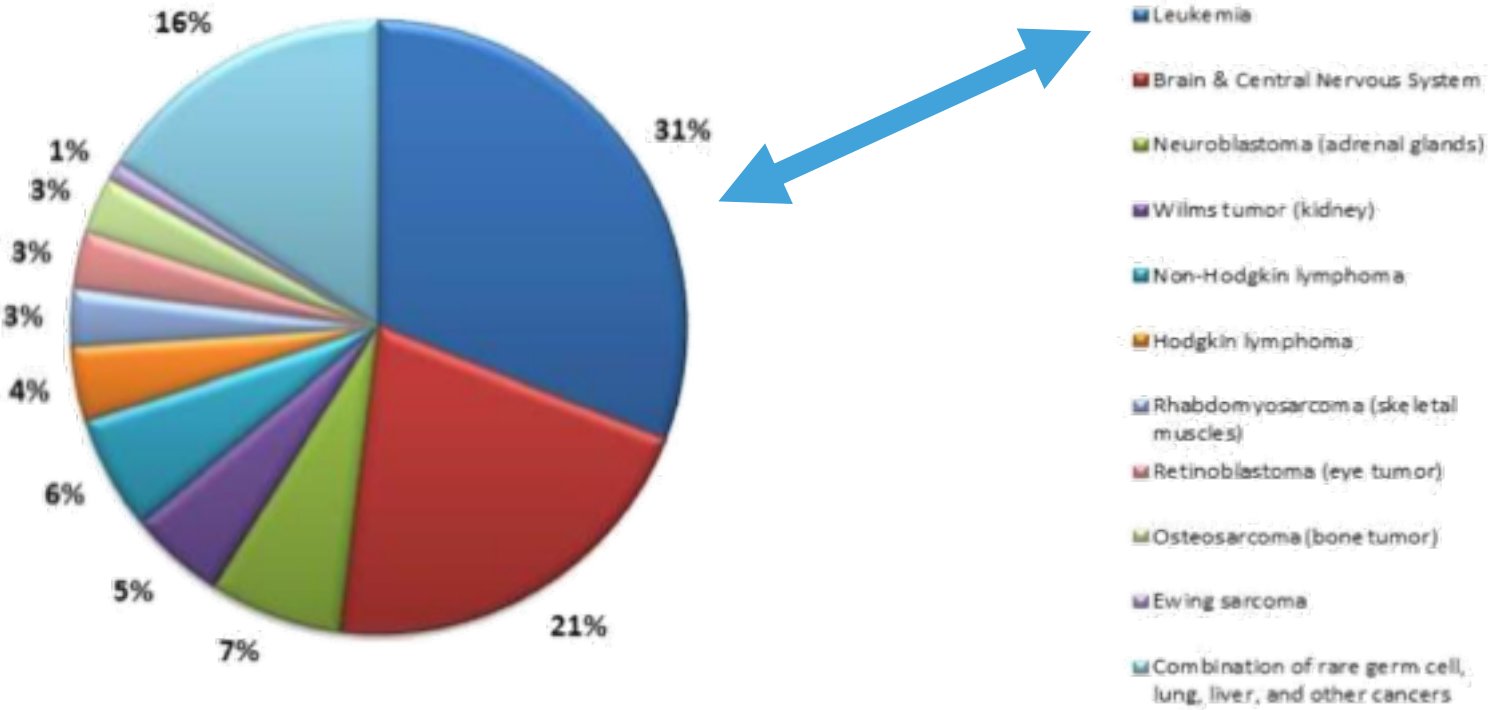
Professor, Departments of pediatrics and pharmacology, University of  
Montreal



**FEAM Conference 2018**  
on Precision Medicine  
and Personalized Health

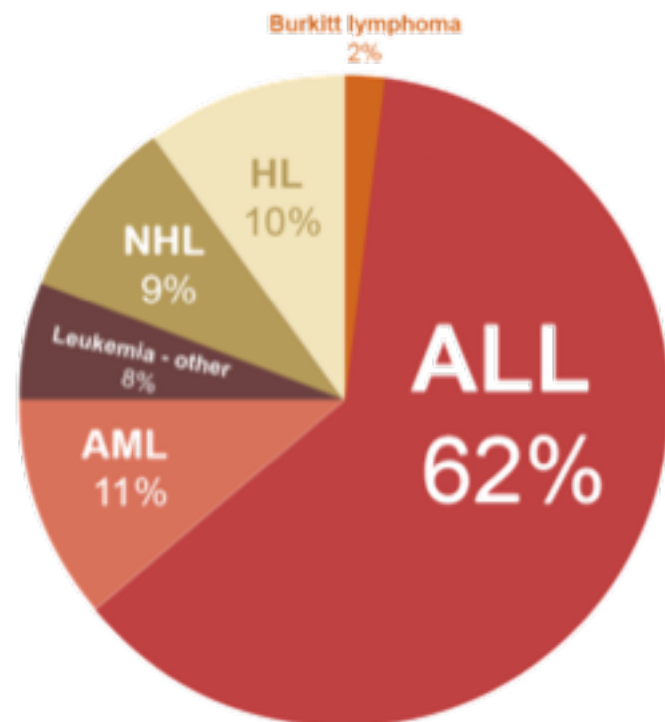
28 September 2018  
Geneva, Switzerland

# Most common childhood cancers



# New Cases of Blood Cancers

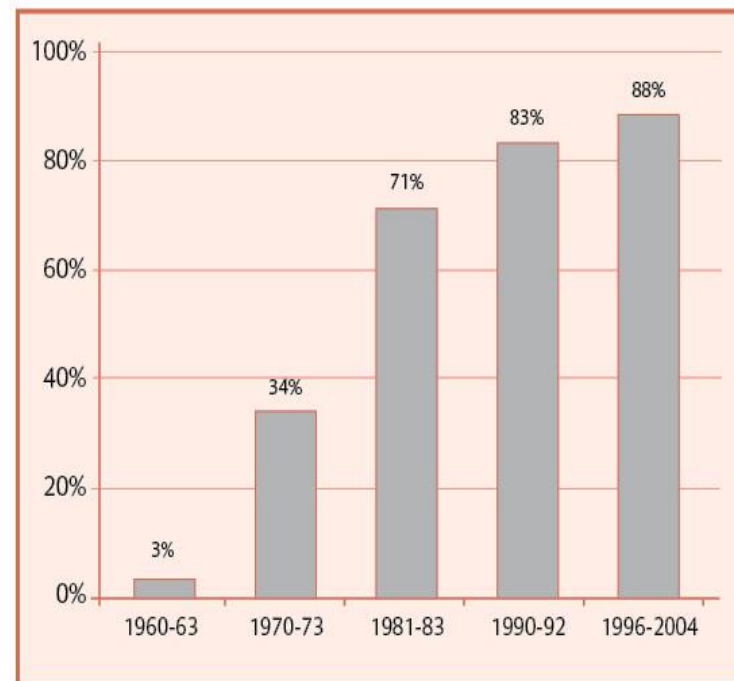
in Children Age 0-14



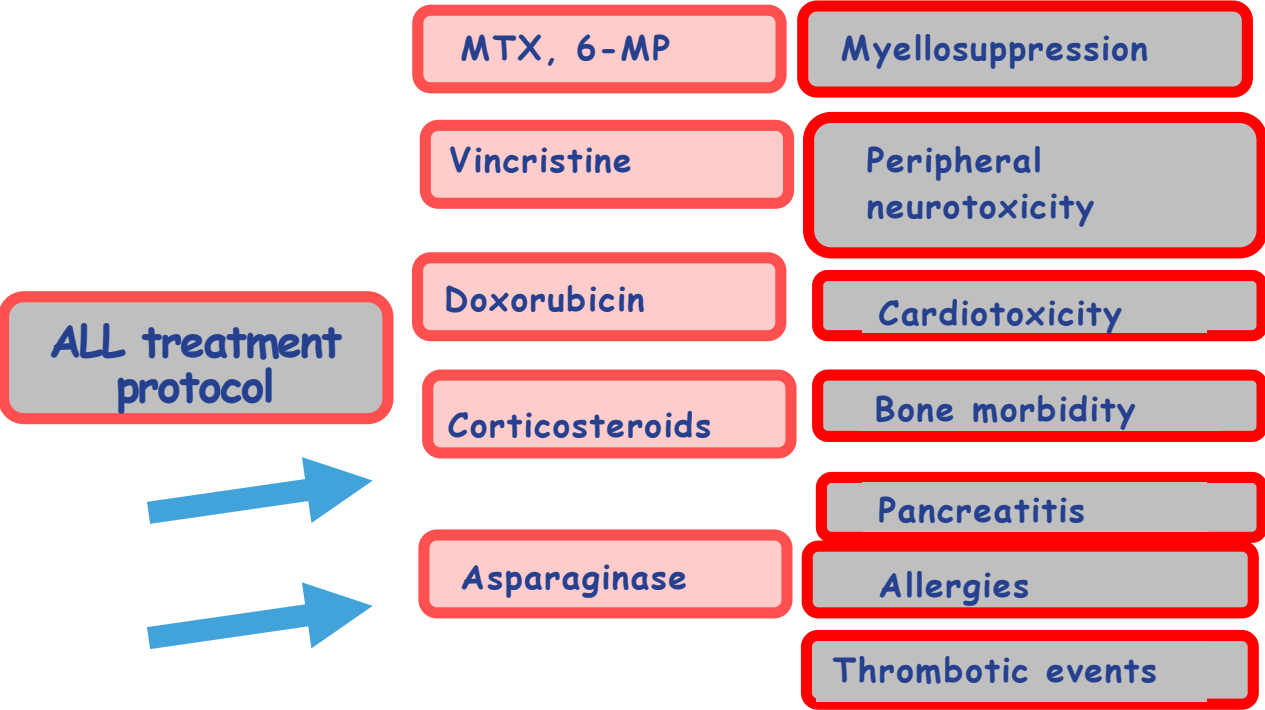
Canadian Cancer Society's Advisory Committee on Cancer Statistics, Canadian Cancer Statistics 2014. Toronto, ON; Canadian Cancer Society; 2014.

# overall survival

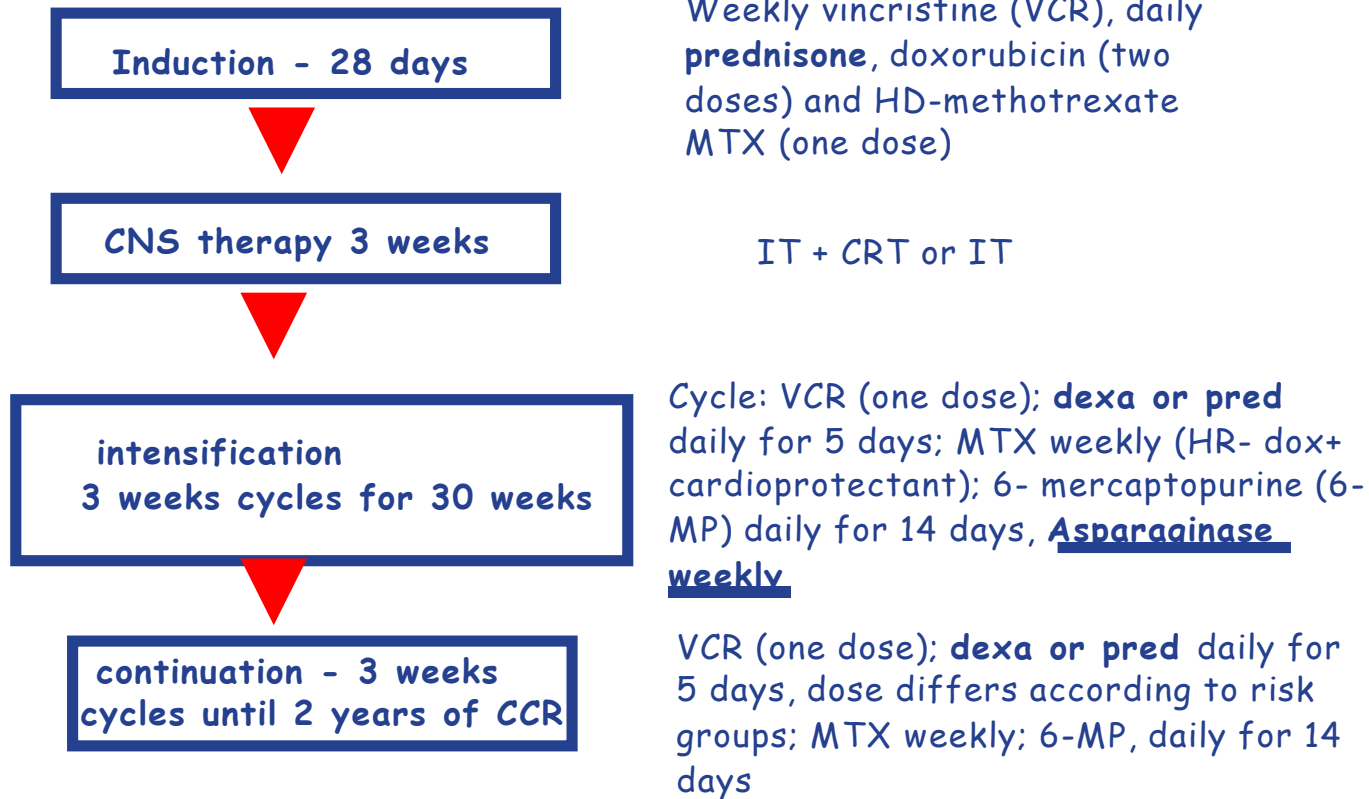
*Improvement of overall survival at 5 years in pediatric patients (<15 years)*



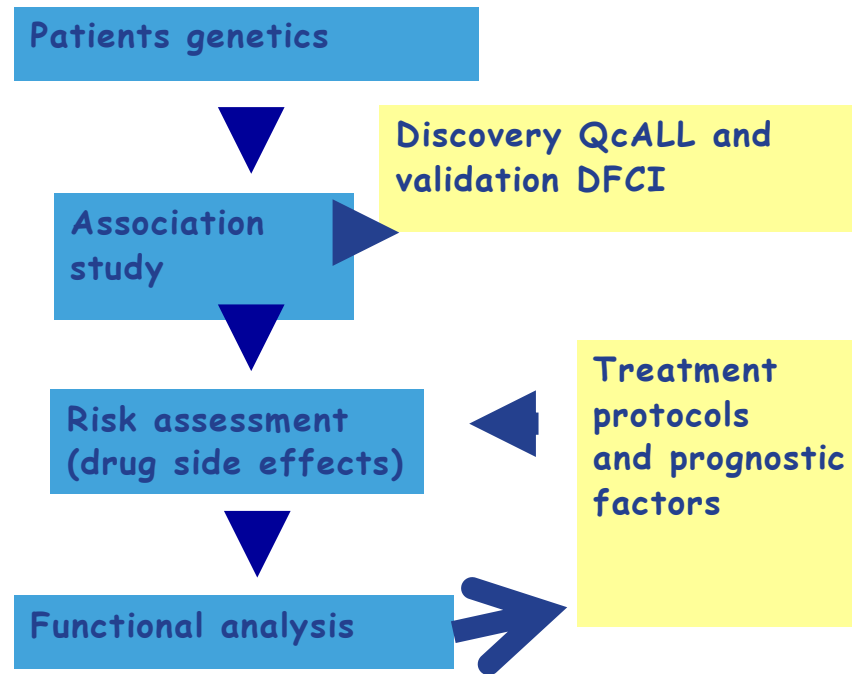
# Toxicities associated with ALL treatment



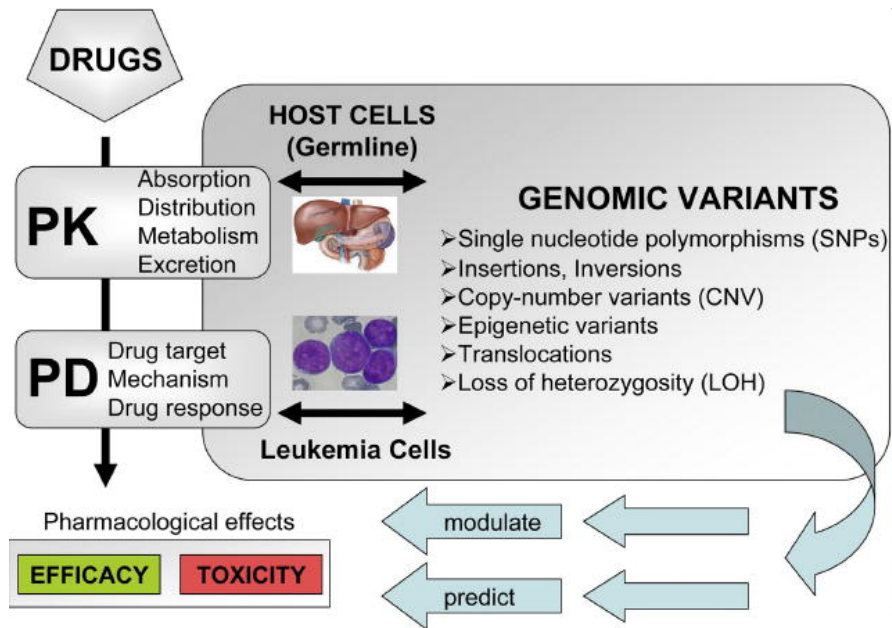
# ALL treatment protocol (DFCI)



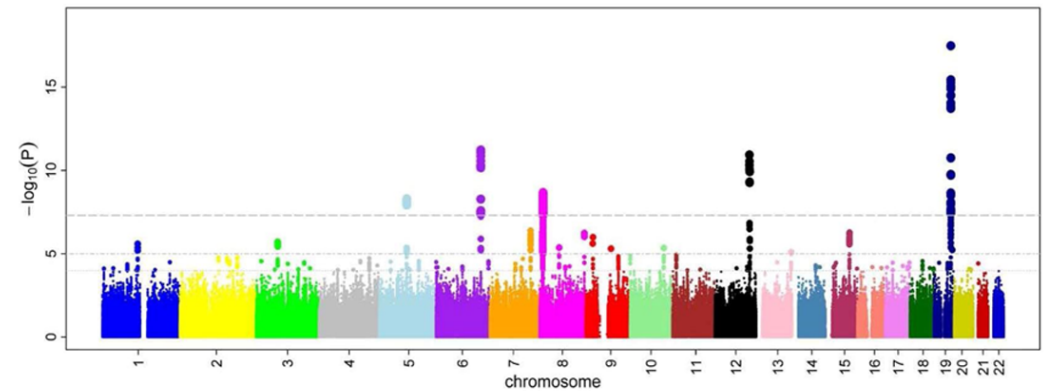
# Pharmacogenetics of childhood leukemia



# Pharmacogenetics of childhood leukemia



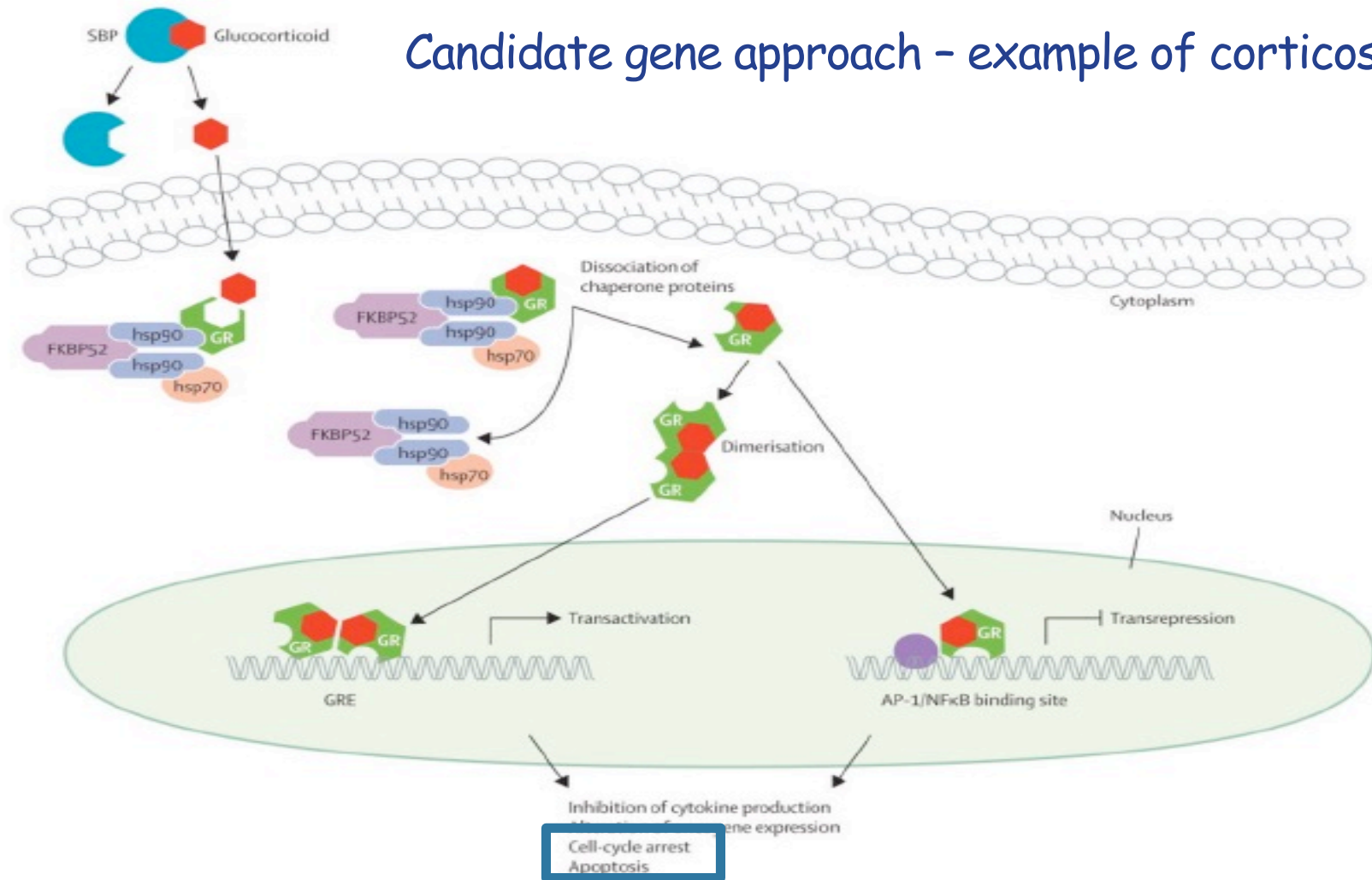
Candidate gene approach



Genome/exome-wide approaches



# Candidate gene approach - example of corticosteroids

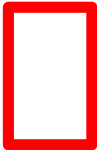
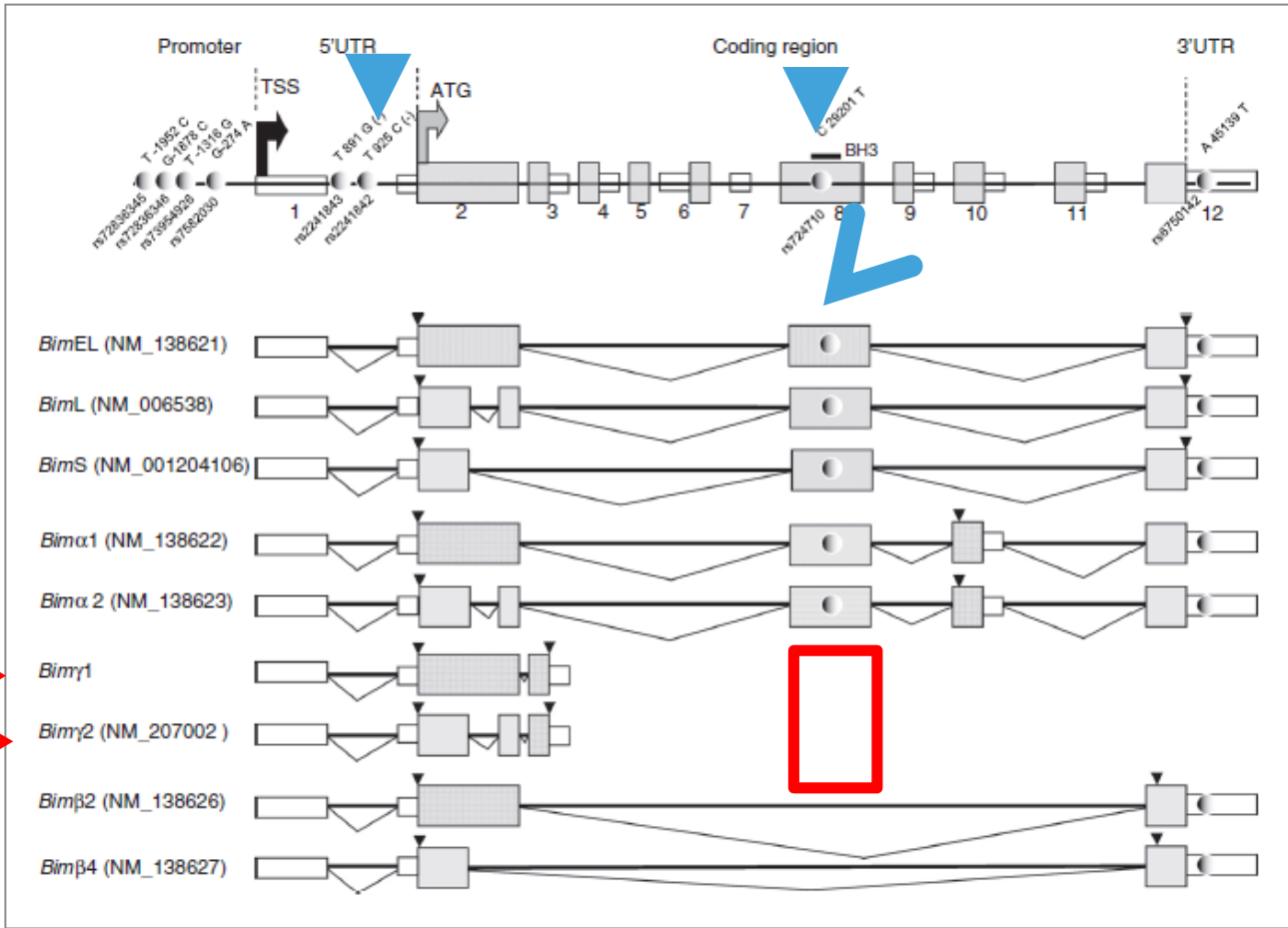


## Candidate gene approach - Osteonecrosis

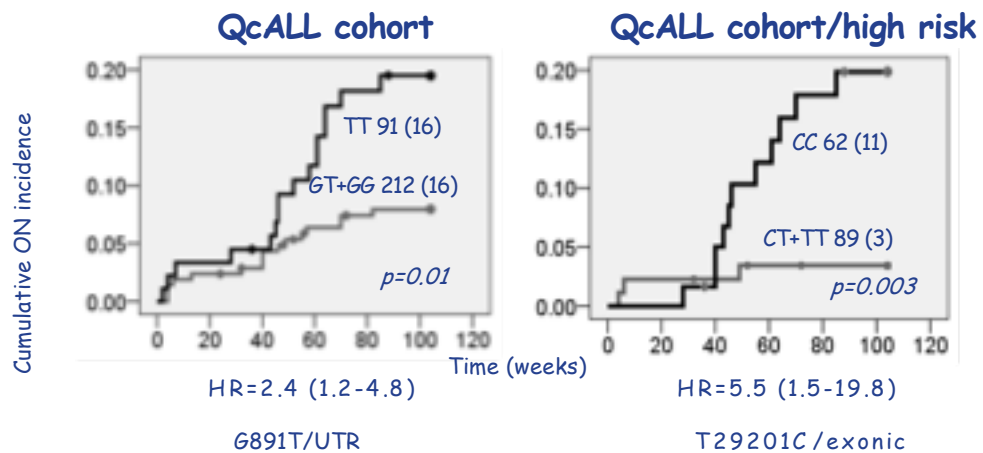
- one of the major complications of childhood ALL treatment
- symptomatic ON causes severe pain, joint damage and articular collapse
- CS - change the number or function of osteoclasts/osteoblasts, leading to bone loss by increased bone resorption

## Candidate gene approach - example of Bim

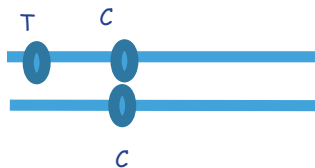
- Microarray profiling in CS-induced apoptosis models has shown that CS exposure induces or represses the transcription of pro- or anti-apoptotic genes including pro-apoptotic Bim encoded by *BCL2L11 gene*
- Differentially expressed between cells that are resistant or sensitive to CS
- SNPs in Bim gene have been shown to influence survival probabilities in ALL patients
- Bim has been also described as a key regulator of osteoblast apoptosis



# Association analysis between Bim gene and ON

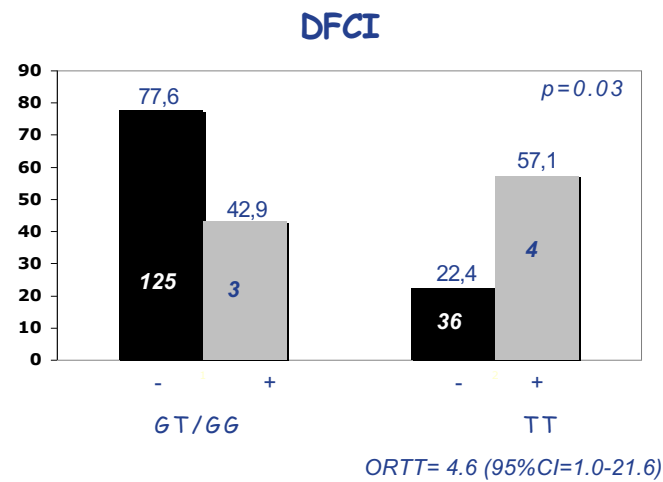


G891T/UTR



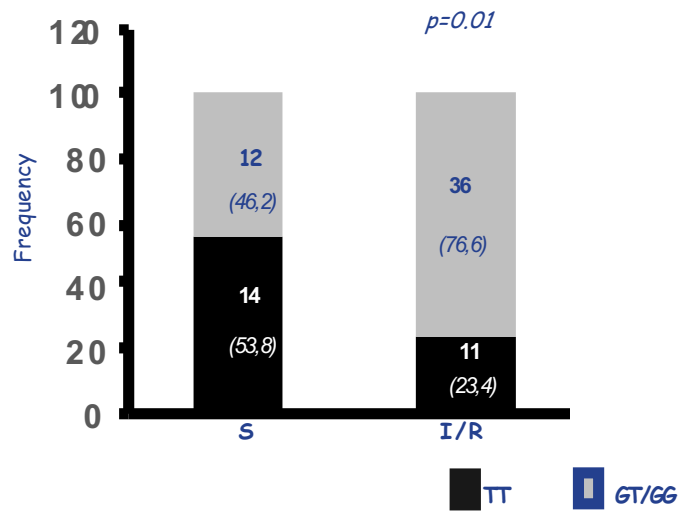
T29201C/exonic

haplotypes

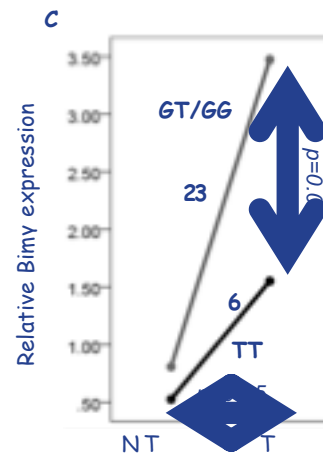


■ ON-  
 ■ ON+

# The effect on in-vitro cellular viability and gene expression

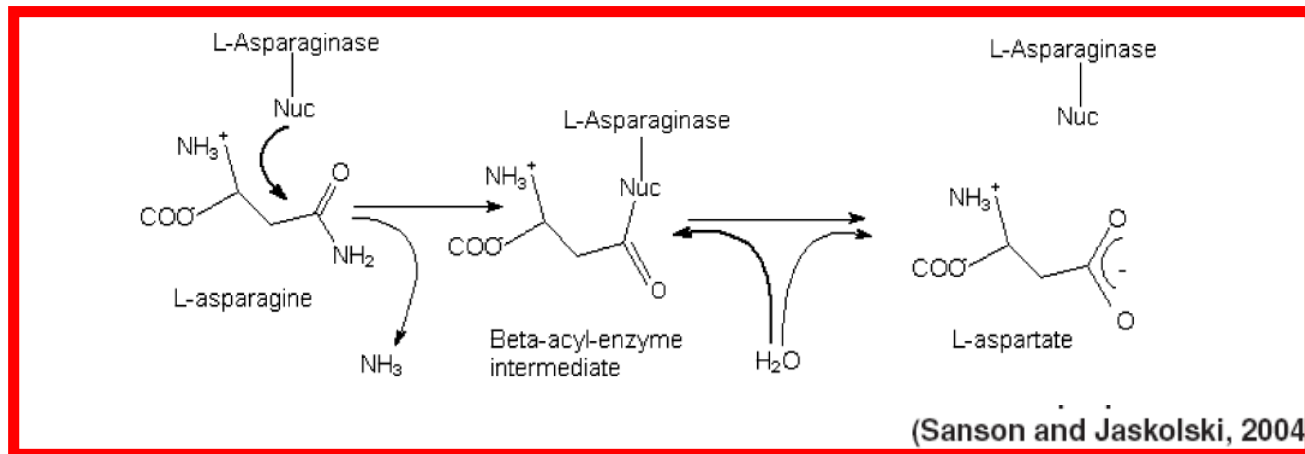


In-house built library of CS IC50 for 70+ LCLs



Bim  $\gamma$  in LCLs

## Asparaginase -example of exome wide approaches

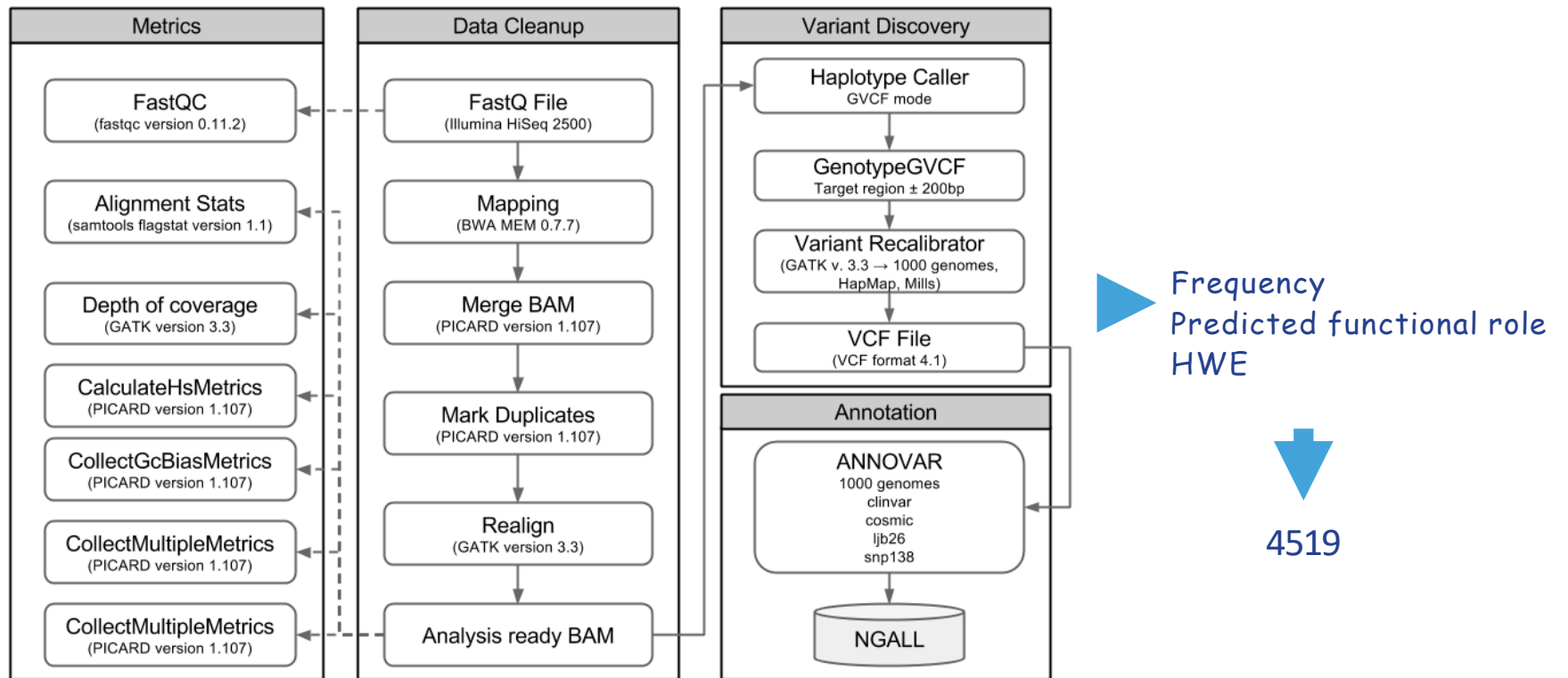


derived from *E.coli* or *Erwinia* species. PEG  
ASNase - polyethylene glycosylation of the native *E.coli*-derived enzyme

- catalyzes the conversion of L-asparagine to aspartic acid and ammonia depleting the circulating levels of asparagine
- the rationale behind ASNase treatment
- ALL leukemic cells synthesize low quantity of Asn -dependent on circulating Asn levels which are depleted by ASNase treatment.

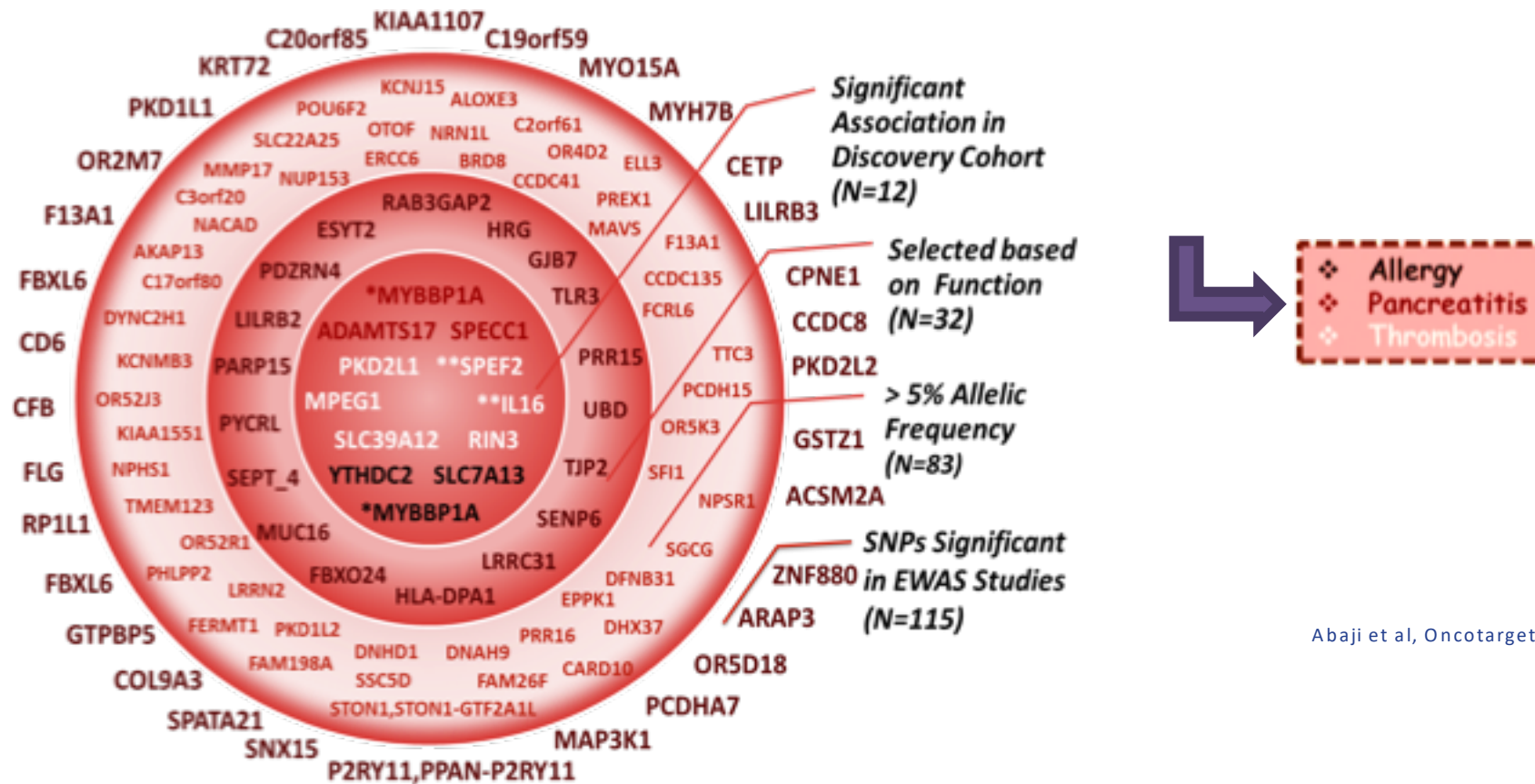
# Whole Exome Sequencing-WES

## Pipeline DNASEQ germline

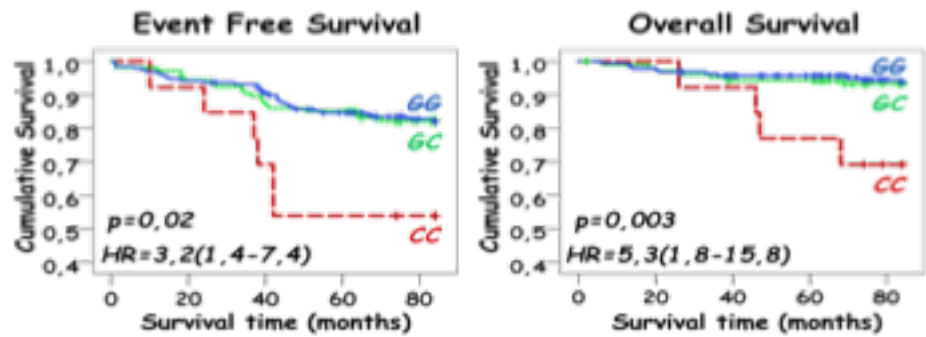
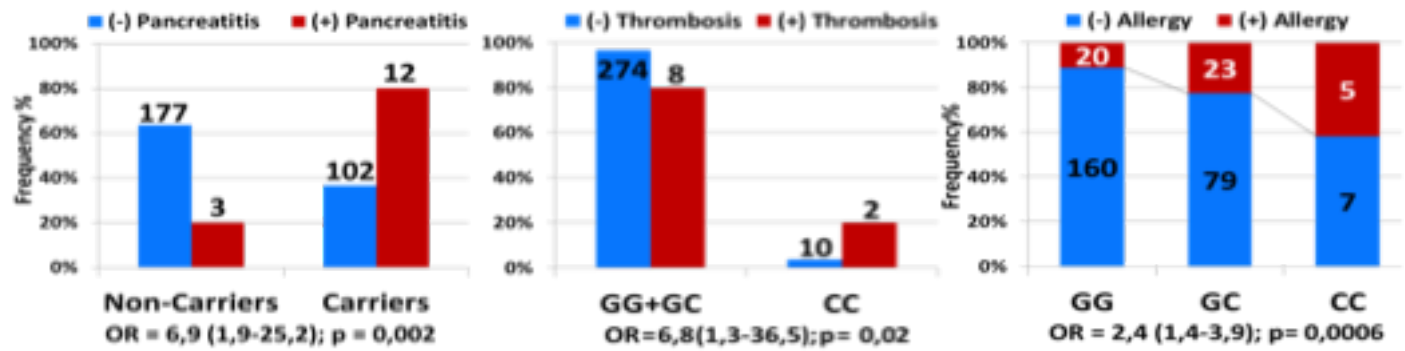




# Exome-Wide Association Study (EWAS) with asparaginase complications



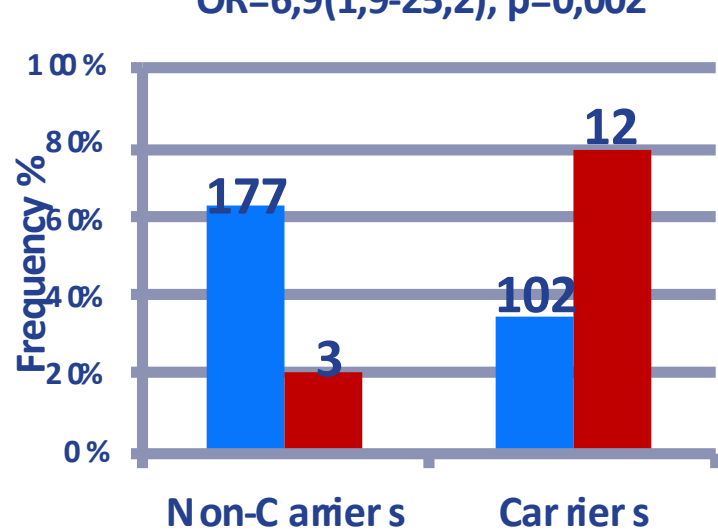
# rs3809849\_MYBBP1A



# rs3809849\_MYBBP1A vs. Pancreatitis

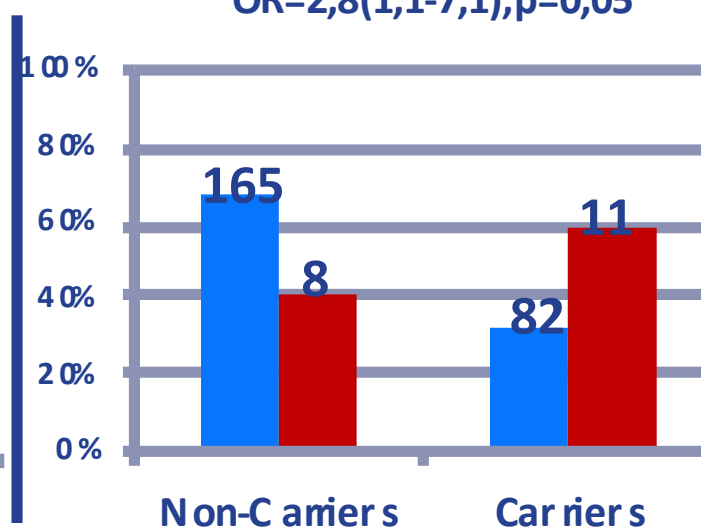
## Discovery Cohort

OR=6,9(1,9-25,2); p=0,002



## Replication Cohort

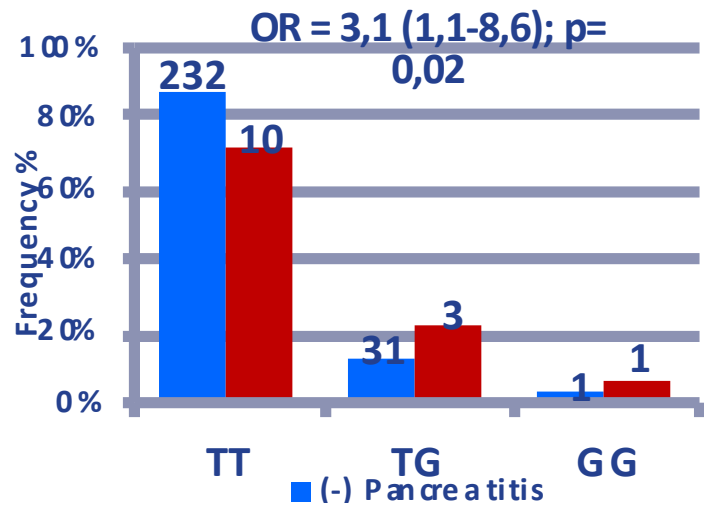
OR=2,8(1,1-7,1); p=0,05



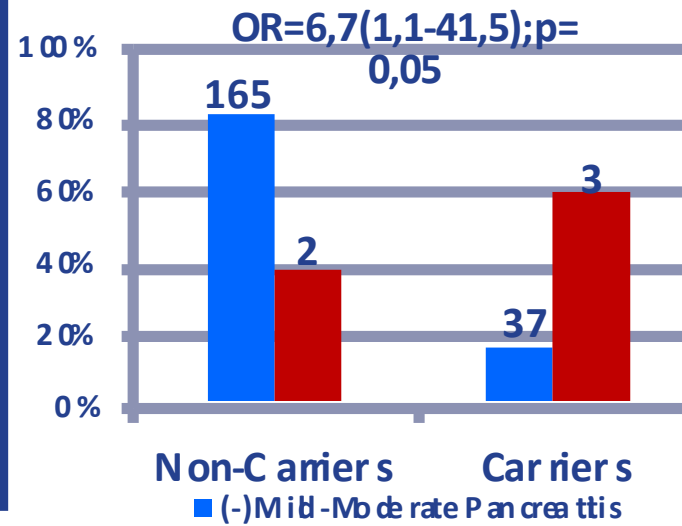
■ (-) Pancreatitis    ■ (+) Pancreatitis

# rs11556218\_IL16 vs. Pancreatitis

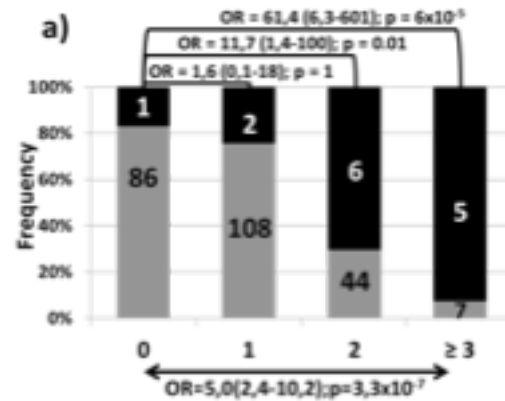
## Discovery Cohort



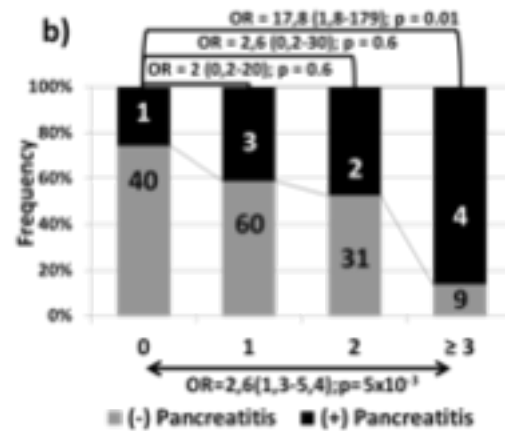
## Replication Cohort



# Combined effect model

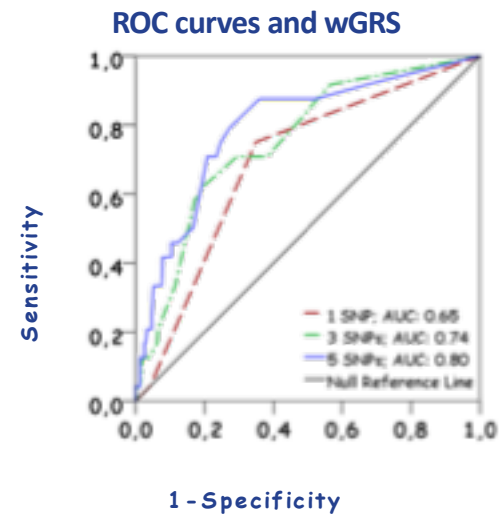
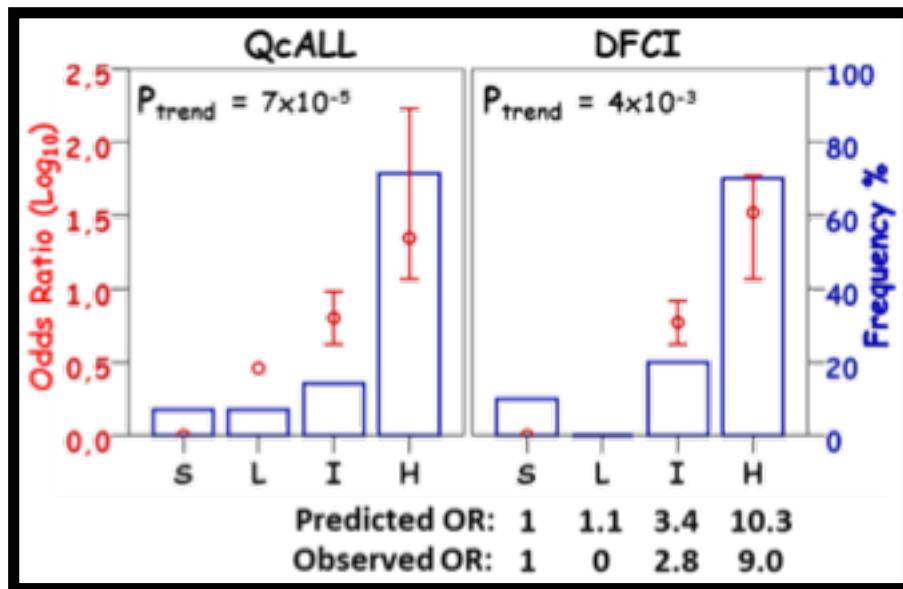


QcALL



DFCI

# Weighted genetic risk score (wGRS)



Cohort	AUC $\pm$ SD.	95% CI	P	Sensitivity	Specificity
QcALL	0,80 $\pm$ 0,062	68,1 ~ 92,6	$1 \times 10^{-4}$	71%	81%
DFCI	0,78 $\pm$ 0,076	63,0 ~ 92,9	$3 \times 10^{-3}$	70%	77%
Combined	0,80 $\pm$ 0,049	70,1 ~ 89,1	$1 \times 10^{-6}$	71%	79%

# They have pertinent function

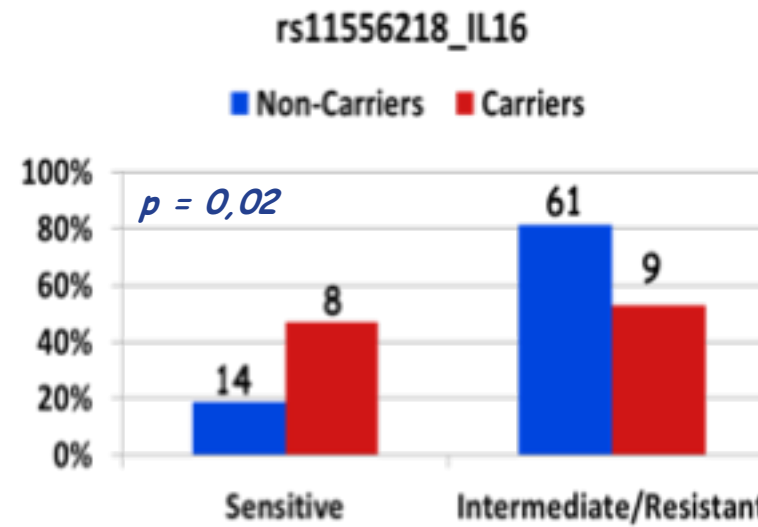
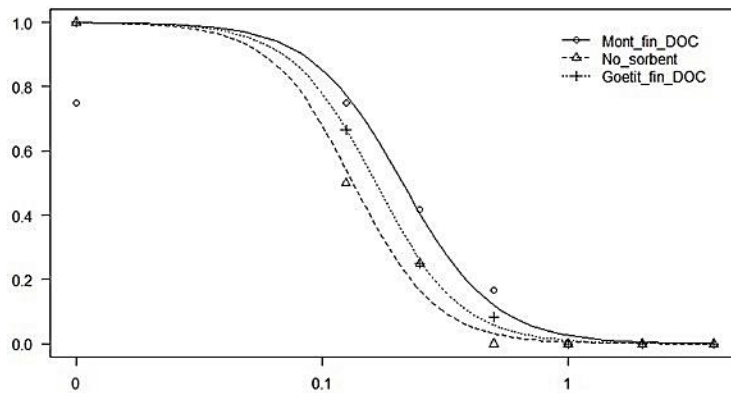
## **MYBBP1A gene**

- encodes a nucleolar transcriptional regulator (Myb-Binding Protein 1A)
- plays a role in many cellular processes
  - tumor suppression,
  - cell cycle and mitosis
  - co-repressor of the nuclear factor kappaB

## **IL16 gene**

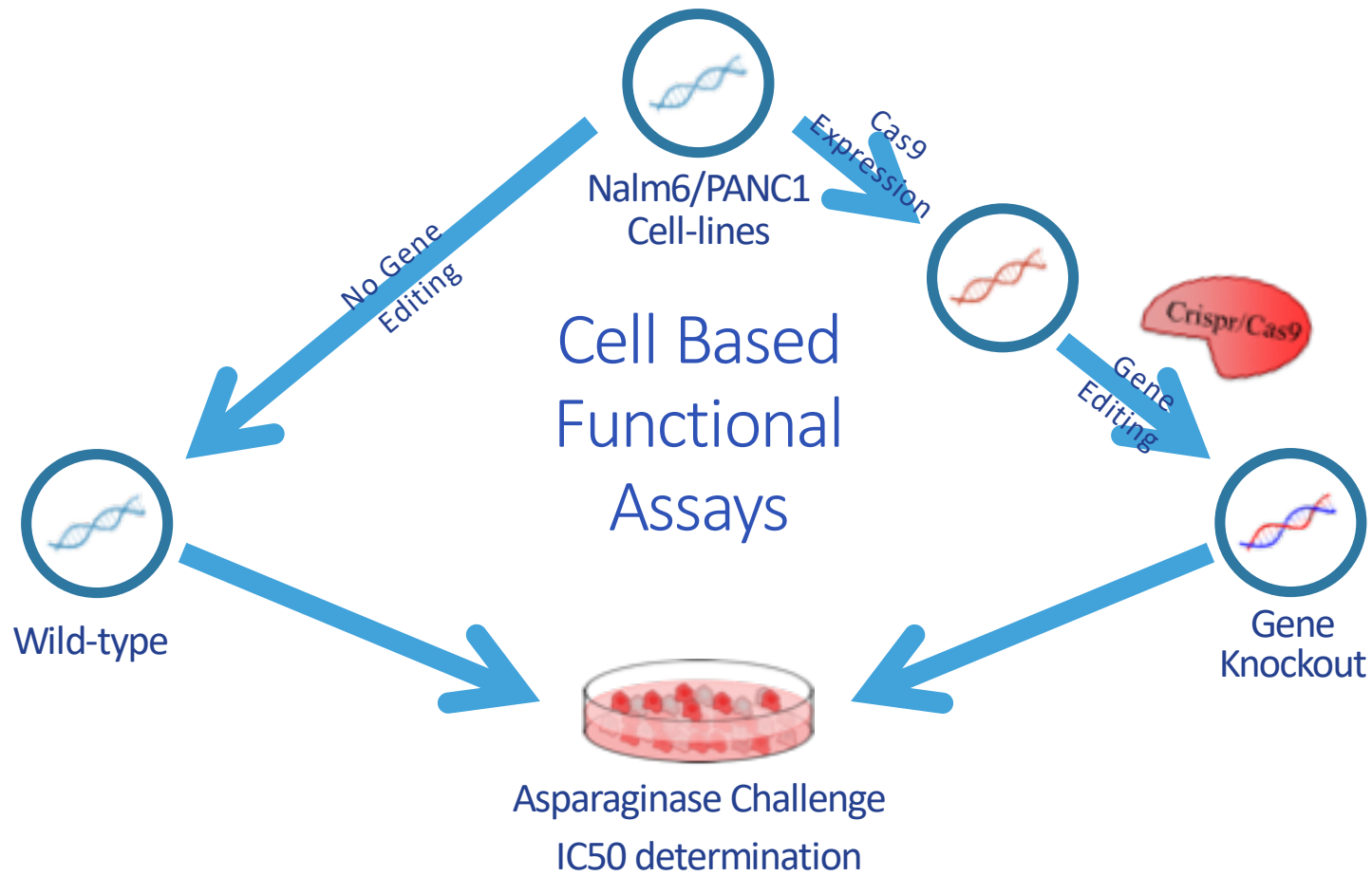
- encodes for a multifactorial cytokine
- involved in inflammatory and autoimmune diseases
- cell cycle control and cancer
- **rs11556218**  
associated with a wide range of conditions (Coronary Artery Disease, Ischemic Stroke, Systemic Lupus Erythematosus, Cancer risk)

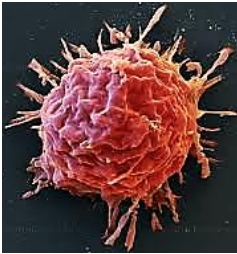
## In-house built library of Asparaginase IC50 for 90+ LCLs



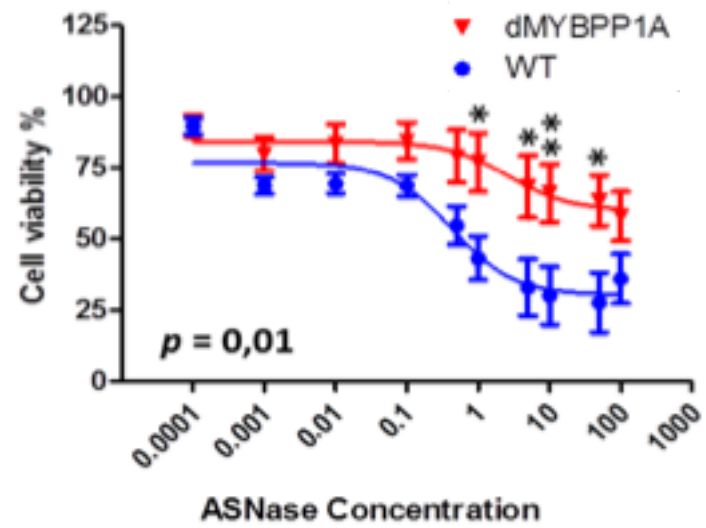


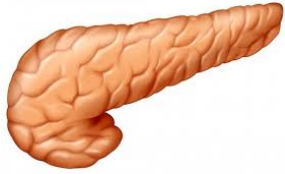
# Gene Knockout Production





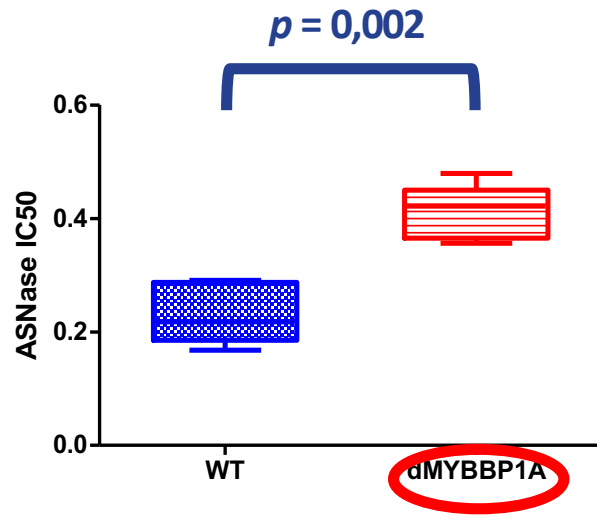
## Nalm6



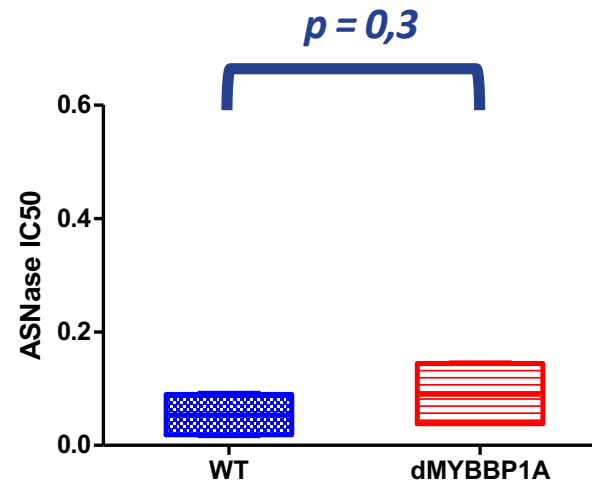


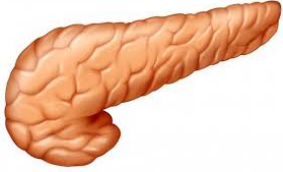
# Panc1 Cells

Day 2

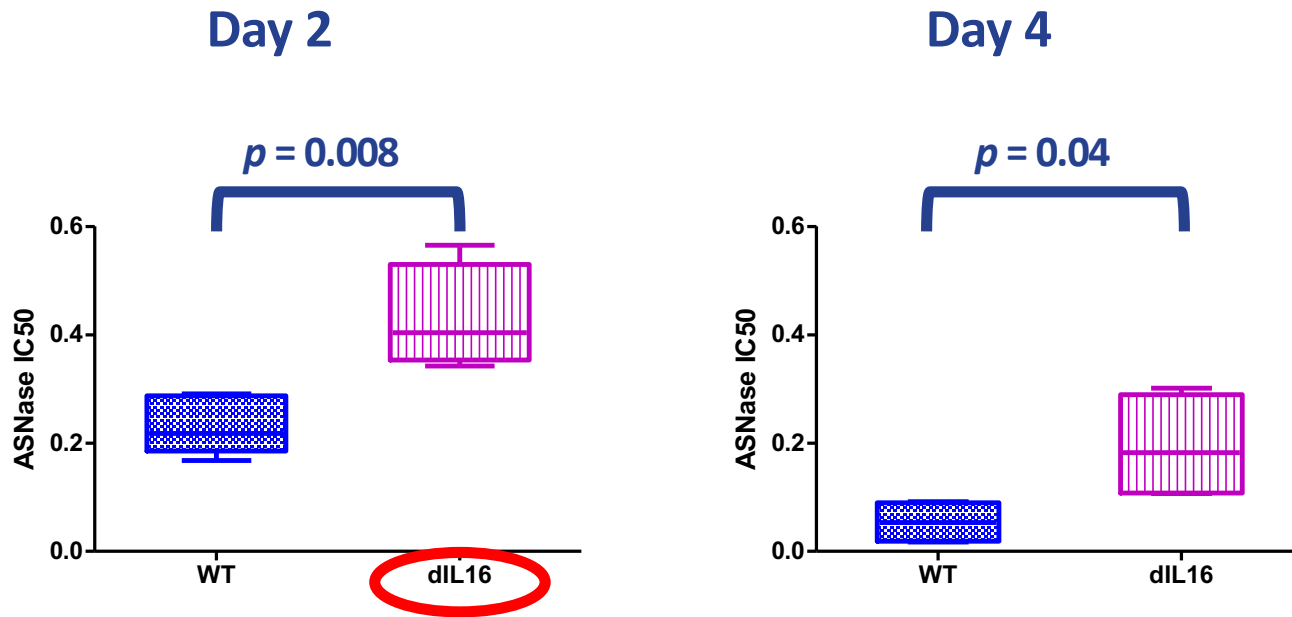


Day 4

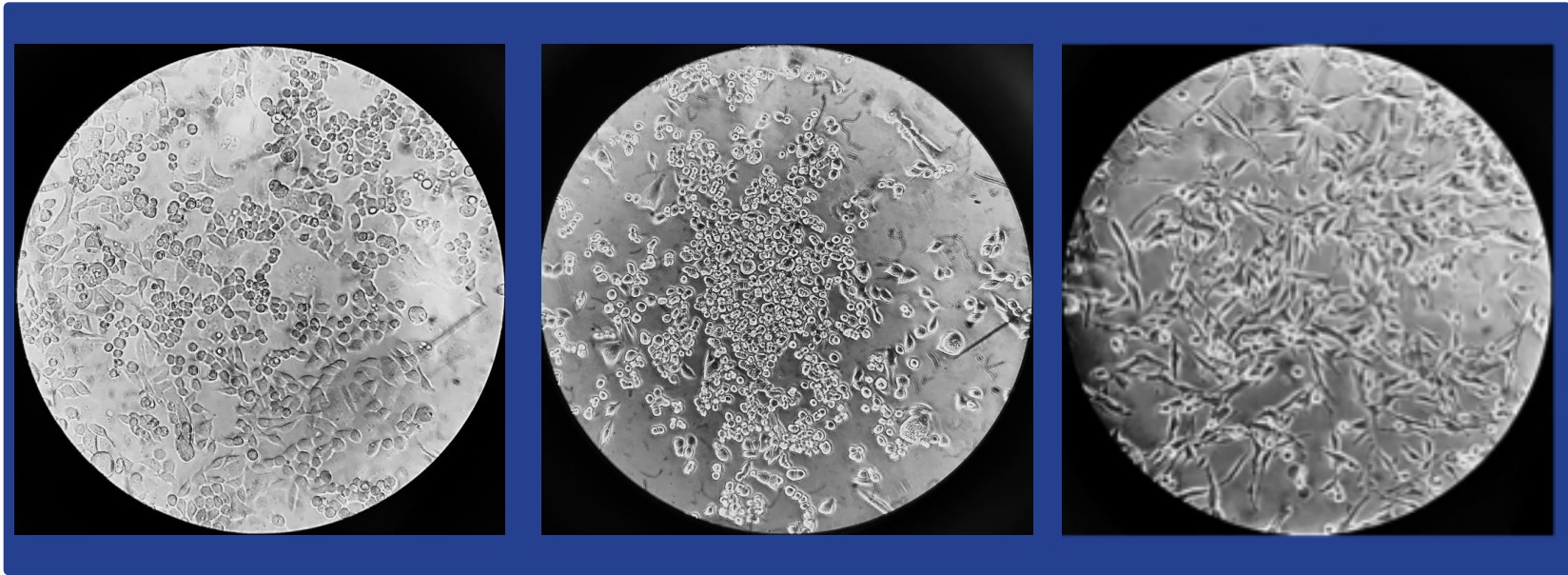




# Panc1 Cells



# Difference in morphology



WT

dMYBBP1A

dIL16

# Acknowledgment

## Project Contributors, CHUSJ:

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