How does recent cancer research influence possible treatments of cancer in Bloom syndrome?
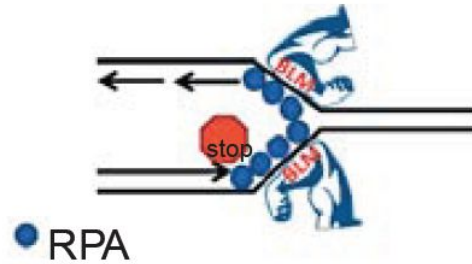
Bloom Syndrome Association

Webinar Session 4
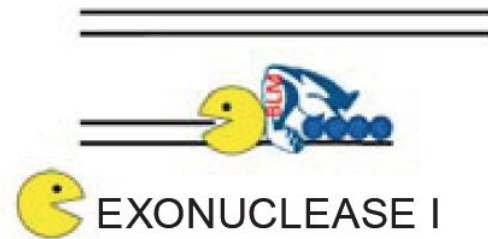
July 22, 2020
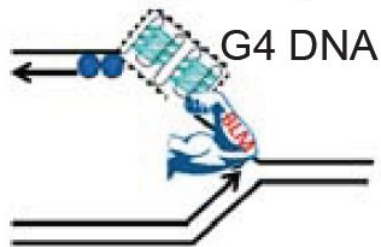
BLM has many functions

A Rescue stalled forks

B Help resect dsDNA

RPA

EXONUCLEASE I

F Unwind pesky DNAs

G4 DNA

Hero of our story

C Dissolve double HJs

TOPOISOMERASE IIIα
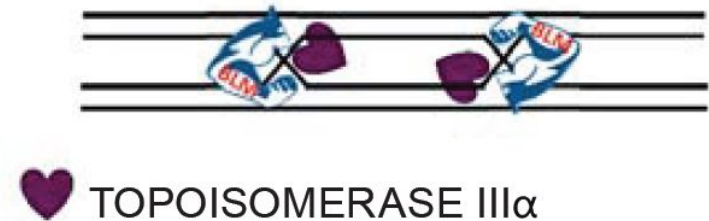
E Separate tangled strands
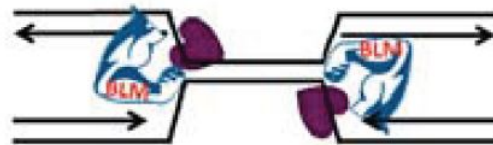
D Dissociate joint molecules

POLYMERASE
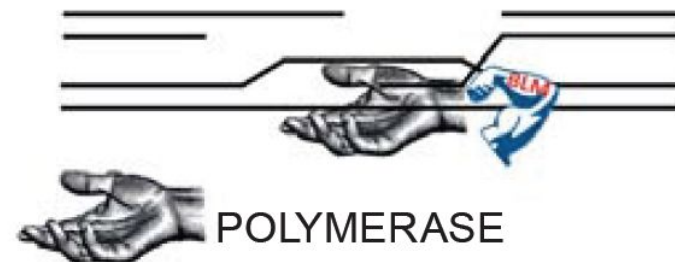
MIND THE GAP

Therapeutic window

For a cancer in a BLM+ person

For normal tissue

Percent of patients responding

Therapeutic window — Efficacy

Therapeutic index

Toxicity

Concentration of drug X in plasma (mg/L)

"Chemogenomics"

Olivieri et al., Cell 2020
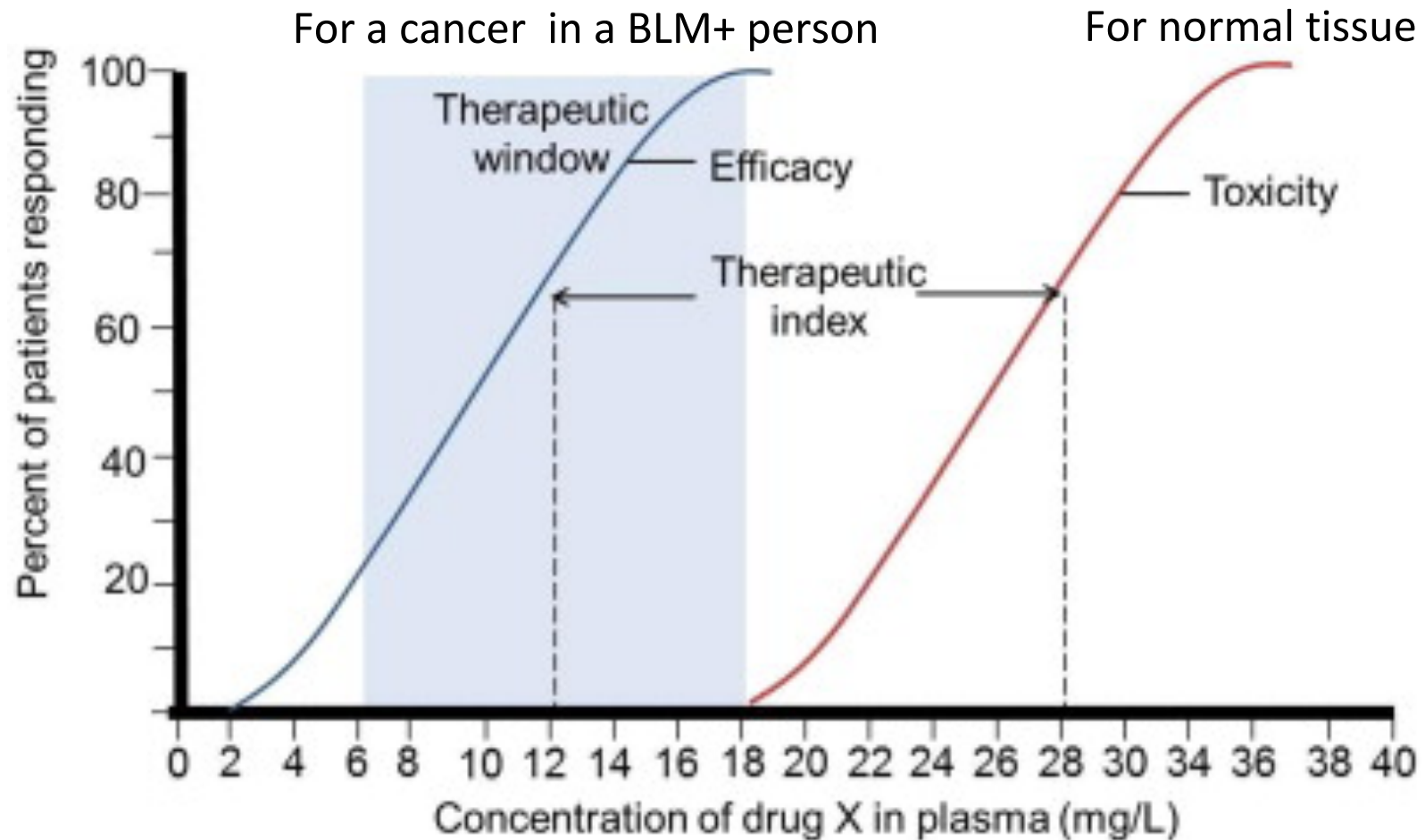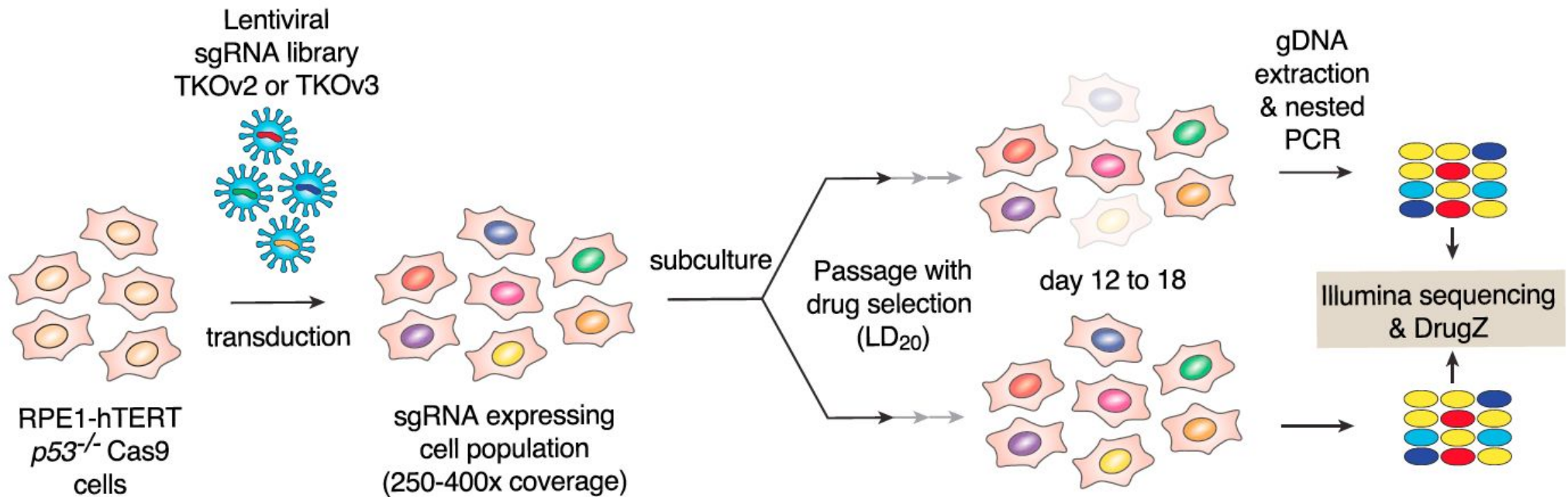
BLM-negative cells are very sensitive to alkylating agents and interstrand-crosslinking (ICL) agents

BLM-negative non-cancerous cell

Cisplatin2	-4.6
Cisplatin3	-3.94
MLN4924	-3.01
illudinS	-2.98
MNNG	-2.39
KBrO3	-2.35
Cisplatin1	-2.28
MMS	-2.19
BPDE	-2.13
HU	-1.4
AZD6738	-1.26
UV	-1.07
ICRF	-1.06
Olaparib	-0.86
Etoposide	-0.57
IR	-0.46
Bleomycin	-0.43
Doxorubicin	-0.41
CD437	-0.24
Calicheamicin	-0.21
CPT2	-0.12
Gemcitabine	0.09
Formaldehyde	0.17
PhenDC3	0.17
PladB	0.34
CPT1	0.55
H2O2	0.67
Trabectedin	0.71
HU2	1.12
Pyridostatin	1.16
Duocarmycin	1.66

Very sensitive

No effect

Resistant

BLM-negative cancer cell
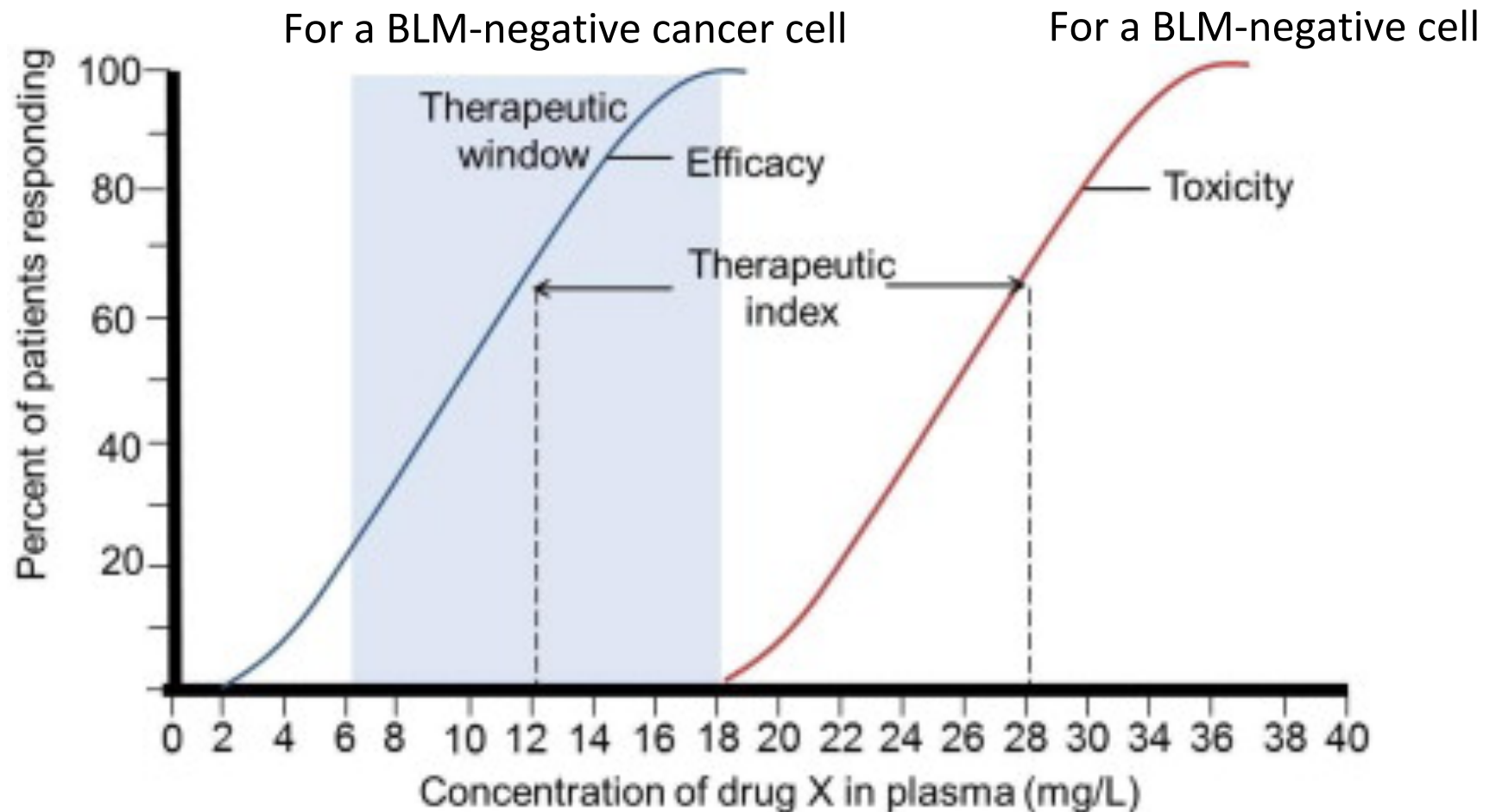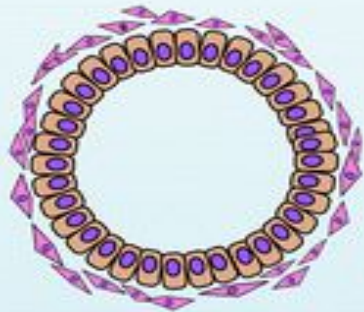
?

The gap is the therapeutic window isn't known for BLM-negative cancers

Common intestinal organoid models

Stem Cell Lines

Normal Intestine

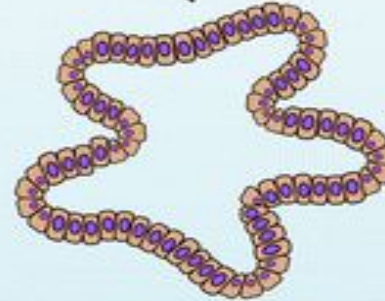CRC tissue

Induced
Intestinal Organoid
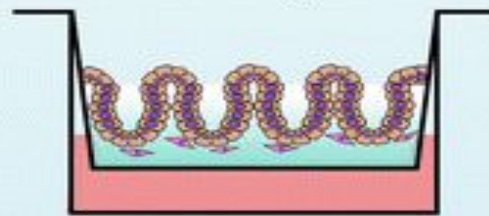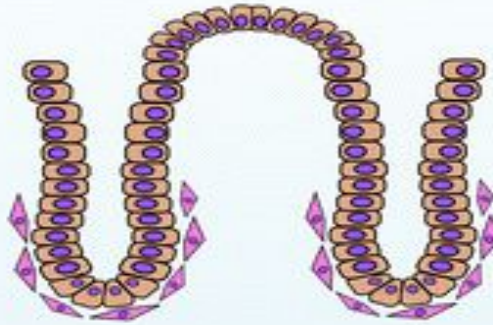
Air Liquid Interface

Genetic
modification

"Mini-gut"
Colonoid/Enteroid

CRC Tumoroid

Day0 Day1   Day3   Day5   Day7   Day10
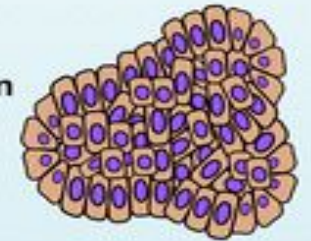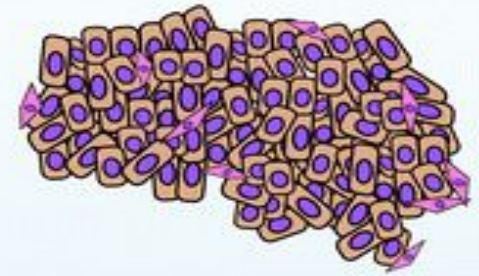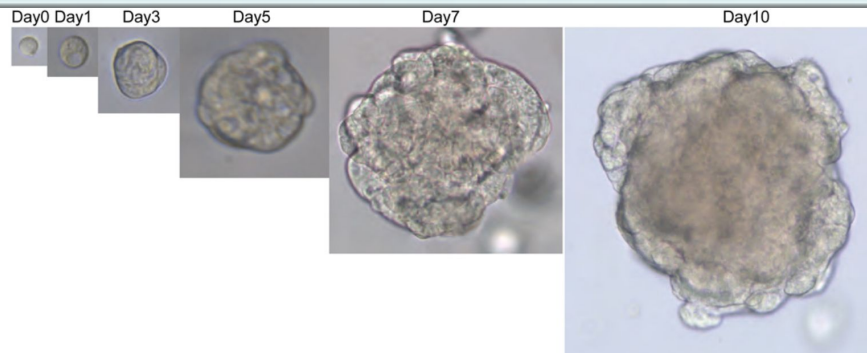
Organoid-based drug screening