Cancer Surveillance and Treatment in Patients with Bloom Syndrome

Bloom Syndrome Association Webinar
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Vivian Y Chang

Mattel Children's Hospital UCLA

Overview

- Cancer surveillance
  - Goals
  - Current recommendations
  - Current challenges and limitations
  - Future directions
- Cancer treatment
  - Current understanding
  - Literature review
  - Example of patients with leukemia from the BSR
  - Future directions

Cancer surveillance

- Overarching goal is to personalize interventions to reduce morbidity and mortality
  - Strive for cancer prevention
  - Early detection through rational and personalized surveillance plans
  - Effective and less toxic therapies
- Pediatric Cancer Predisposition Workshop organized by American Association of Cancer Research (AACR)
  - Published series of surveillance articles in 2017 in *Clinical Cancer Research*
- Health supervision guidelines published in 2018

Cancer surveillance

- Risk for cancer at multiple sites makes cancer surveillance challenging

Cancer	Test
Leukemia	Awareness of signs and symptoms
Lymphoma	Whole body MRI every 1-2 years starting 12-13 years
Colon ca	Colonoscopy once a year starting 10-15 years, plus fecal occult blood testing every 6 months
Breast ca	Breast MRI once a year starting 18 years
Skin ca	Annual dermatology exam
Wilms tumor	Abdominal ultrasound every 3 months until 8 years

Walsh MF, Chang VY, Kohlmann WK, Scott HS, Cunniff C, Bourdeaut C, Molenaar JJ, Porter CC, Sandlund JT, Plon S, Wang LL, Savage S. Recommendations for Cancer Screening and Surveillance in DNA Repair Disorders: A Report from the AACR Childhood Cancer Predisposition Workshop. Clin Cancer Res. 2017 June 12:11.

Cunniff C, Djavid AR, Carrubba S, Cohen B, Ellis NA, Levy CF, Jeong S, Lederman HM, Vogiatzi M, Walsh MF, Zauber AG. Health supervision for people with Bloom syndrome. American Journal of Medical Genetics, Part A, 2018. 176(9), 1872-1881.

Cancer surveillance

- Practical challenges
  - Funding and insurance coverage
  - Lack of technological availability
  - Need expertise in reading images
  - Potential risk of repeated sedation
- Incidental findings
  - Lead to additional, possibly more invasive diagnostic tests
  - Balance between focusing on early evidence of cancer versus not aggressively pursuing every incidental finding

Malkin D, Nichols KE, Schiffman JD, Plon SE, Brodeur GM. The Future of Surveillance in the Context of Cancer Predisposition: Through the Murky Looking Glass. Clin Cancer Res. 2017;23(21):e133-e137.

Cancer surveillance

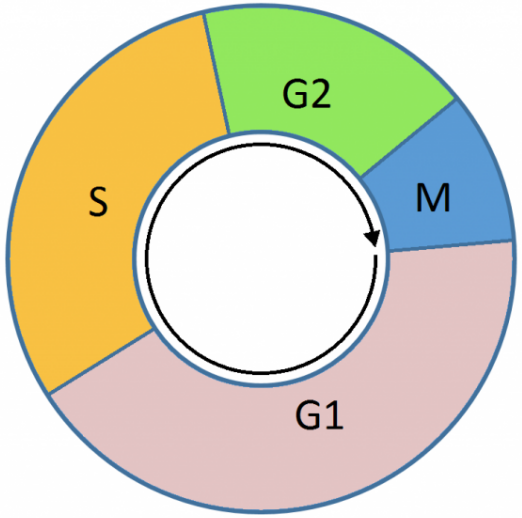
- Scanxiety
  - Anxiety elicited by surveillance both in anticipation of test and in waiting for results
  - May contribute to lack of compliance
  - Recognize and acknowledge signs of anxiety
  - Reduce time to results
  - Empower patients and families
  - Understand that normal scans only mean no tumors could be detected
  - Balance between too much surveillance and not enough surveillance

Cancer surveillance

- Future directions
  - New research efforts to develop more specific and sensitive surveillance tests
  - Circulating tumor DNA (ctDNA) as a surrogate marker of disease
  - Measuring tumor-derived exosomes to detect expressed gene products
  - New tumor markers such as proteins, glycoproteins, or other molecules
  - Improvements in more precise imaging modalities

Cancer treatment

- Increased sensitivity to standard chemotherapy and radiation
  - Few published reports
  - Increased side effects and secondary cancers
  - <= 50% of standard chemotherapy dosing
  - Avoidance of akylating agents (busulfan, melphalan, cyclophosphamide)
  - Avoidance of ionizing radiation



G1 - Growth

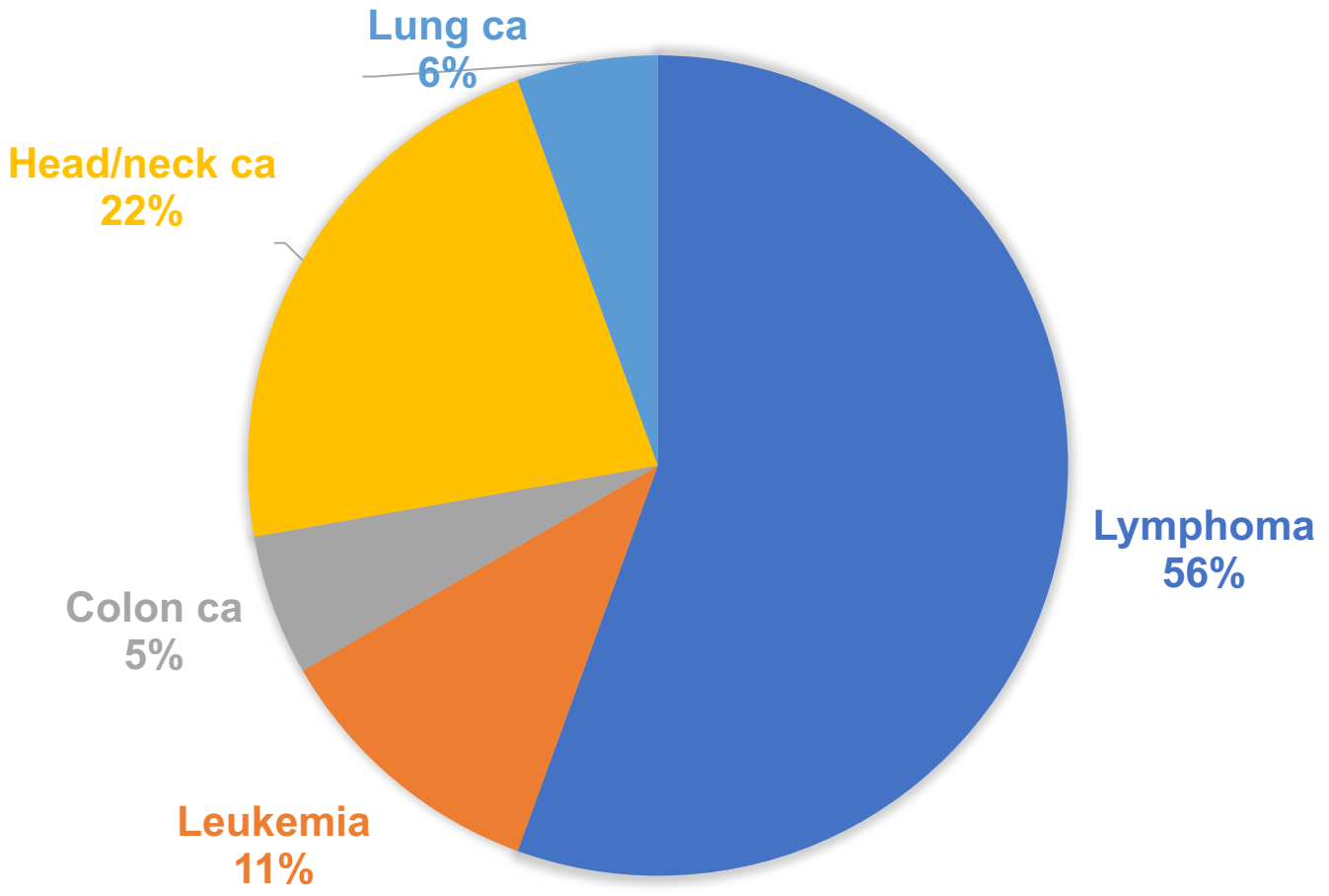
S - DNA synthesis

G2 - Growth and preparation for mitosis

M - Mitosis (cell division)

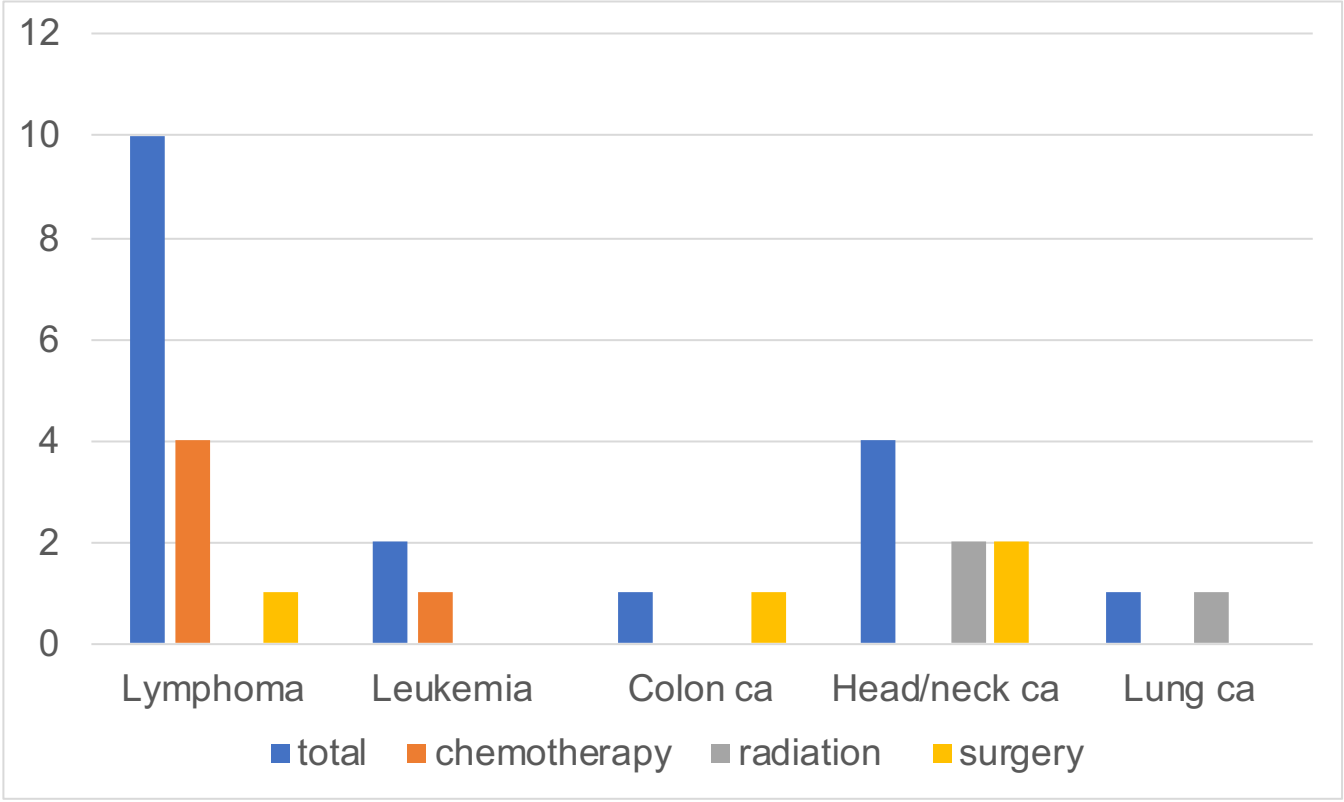
Cancer treatment

- 18 published reports on cancer in patients with Bloom
  - 1989-2016
  - Ages 5-38 years
  - Lymphoma n= 10
  - Leukemia n=2
  - Colon ca n=1
  - Head/neck ca n=4
  - Lung ca n=1



Cancer treatment

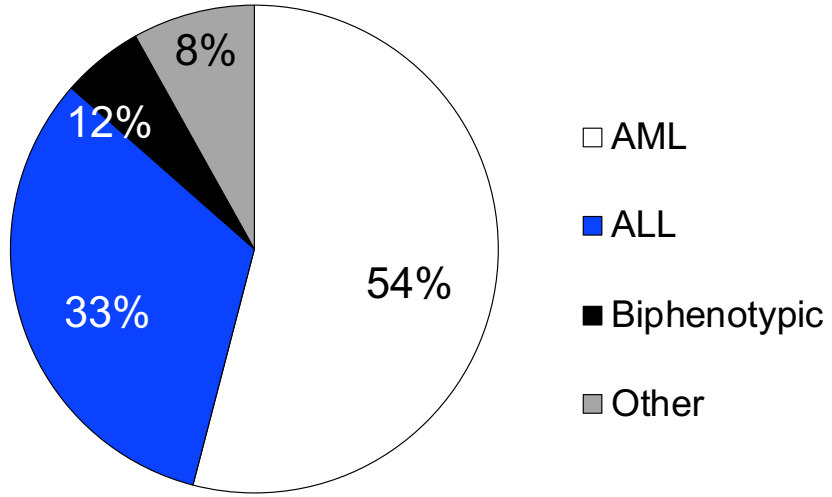
- 18 published reports on cancer in patients with Bloom
  - 5 mention doses of chemotherapy
    - 4 for lymphoma tx
    - 1 for leukemia tx
  - 3 mention doses of radiation
    - 2 for head/neck ca
    - 1 lung ca
  - 4 mention surgery used



Cancer treatment

- 18 published reports on cancer in patients with Bloom
  - Side effects
  - Prolonged bone marrow suppression
    - Fever, infection, bleeding
  - Gastrointestinal complications
    - Nausea, vomiting, mucositis, liver injury
  - Endocrine
    - High blood sugars
  - Strictures after radiation

Cancer treatment



- Registry data on patients with leukemia
  - 37 patients with leukemia
  - Treatment regimen, side effect profile, disease status

	AML	ALL	Biphenotypic
Full dose	4 (20%)	0	0
Modified or omitted dose	4 (20%)	4 (33%)	0
Unknown	9 (45%)	8 (67%)	2 (100%)
No treatment	3 (15%)	0	0

Cancer treatment

- Registry data on patients with leukemia
  - 37 patients with leukemia
  - Treatment regimen, side effect profile, disease status

Toxicity	AML	ALL
Elevated Blood Sugar	0	4 (33%)
Fever Infection	3 (15%)	5 (42%)
Liver Injury Transaminitis	0	2 (17%)
Nausea/Vomiting	1 (5%)	0
Prolonged Bone Marrow Suppression	1 (5%)	6 (50%)
Sepsis	2 (10%)	3 (25%)
Mucositis	1 (5%)	0

Cancer treatment

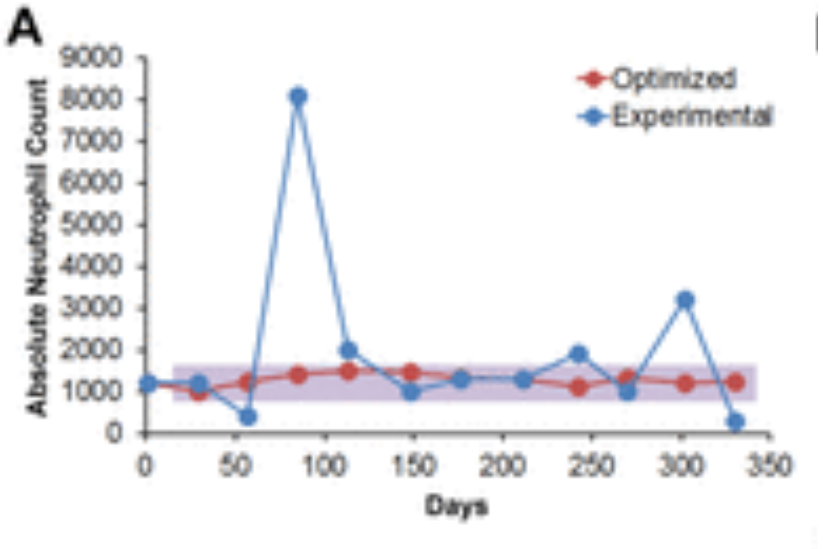
- Future directions
  - Systematically collect detailed dose, side effects, and response information

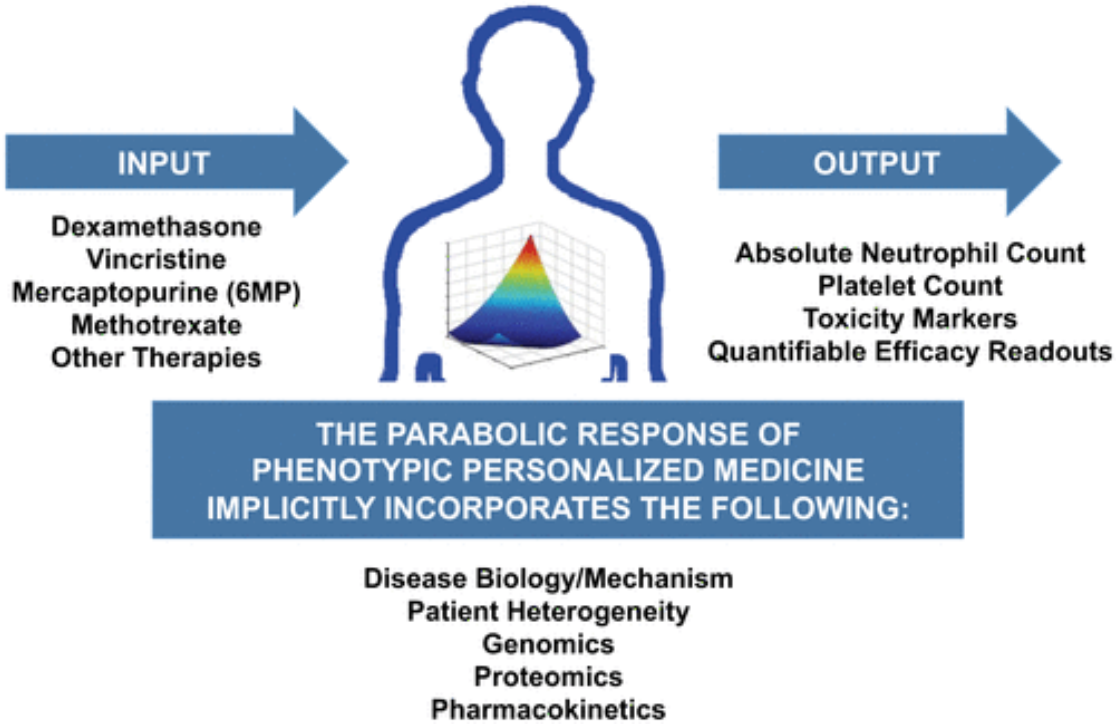
Cycle	Medication	Standard dose	Prescribed dose	Disease status at end
Cycle 1	Venetoclax	240-360mg/m2/dose, days 1-28	200mg/day, days 1-28	80% blasts
	Azacitidine	75mg/m2, days 1-7	75mg/m2/dose, days 1-7	
Cycle 2	Fludarabine	30mg/m2/dose, days 1-5		30-40% blasts
modified FLAG	Cytarabine	2000mg/m2/dose, days 1-5	750mg/m2	
	Gemtuzumab	3mg/m2/dose, day 6	3mg/m2	
	G-CSF	5mcg/kg/dose, days 1-5, restart day 15		
Cycle 3	Fludarabine	30mg/m2/dose, days 1-5		90% blasts, CNS positive
modified FLAG	Cytarabine	2000mg/m2/dose, days 1-5	1400mg/m2	
	Gemtuzumab	3mg/m2/dose, day 6		
	G-CSF	5mcg/kg/dose, days 1-5, restart day 15		
Cycle 4	CPX-351 (Liposomal daunorubicin/cytarabine)	135 Units/m2/dose	44mg/m2	refractory disease
Cincinnati	Venetoclax		200mg	

Chemotherapy Step	Medication	Standard dose	Prescribed dose	Side effects
Induction	Vincristine	1.5mg/m2/dose, days 1, 8, 15, 22	0.6-0.9mg/m2/dose, days 1, 8, 16	bronchospasm, hearing loss, severe pain and severe neuropathy, day 22 held
modified AALL01P1	Prednisone	30mg/m2/dose BID, days 1-28	30mg/m2/dose BID, days 1-28	hyperglycemia requiring insulin
	Peg-asparaginase	2500 IU/m2, day 4	2500 IU/m2, day 4	
	Intrathecal Ara-C	70mg, day 1	70mg, day 1	
	Intrathecal Methotrexate	15mg, days 8, 29	15mg, days 15, 29	days 8 and 22 held due to subdural hematoma
Consolidation	Ara-C	75mg/m2/dose, days 1-4, 8-11, 29-32, 36-39	56.25mg/m2/dose, days 1-3, 8-11	prolonged pancytopenia requiring neupogen
modified AALL01P1	6MP	60mg/m2/dose, days1-14, 29-42	30-60mg/m2/dose, days 1-5	thrombocytopenia after day 2, requiring dose reduction
	Vincristine	1.5mg/m2/dose, days 15, 22, 43, 50	not given	dose skipped due to severe neuropathy
	Peg-asparaginase	2500 IU/m2/dose, days 15, 43	2500 IU/m2/dose, day 15	
	Intrathecal Methotrexate	15mg, days 1, 8, 15, 22	7.5mg, days 1, 8, 15, 22	required ommaya placement and dose reduced for ommaya infusion, day 15 delayed due to pneumonia
Interim Maintenance	Vincristine	1.5mg/m2/dose, days 1, 11, 21, 31, 41	0.45-0.6mg/m2/dose, days 1, 11, 21, 31	pain and infection
modified AALL01P1	Methotrexate	100mg/m2/dose, days 1, 11, 21, 31, 41	40-50mg/m2/dose, days 1, 11, 31	delays due to strep infection and pneumonia
	Peg-asparaginase	2500 IU/m2/dose, days 2, 22	2500 IU/m2/dose, days 2, 32	delayed due to hypertriglyceridemia
	Intrathecal Methotrexate	15mg, days 1, 8, 15, 22	7.5mg, days 1, 31	dose reduced for ommaya infusion
Delayed Intensification				skipped due to septic shock with acinetobacter
Maintenance #1				
Modified AALL0232	Vincristine	1.5mg/m2/dose, days 1, 29, 57	0.6mg/m2/dose, days 1, 29, 57	
	Prednisone	20mg/m2/dose BID, days 1-5, 29-33, 57-61	20mg/m2/dose BID, days 1-5, 29-33, 57-61	
	6MP	75mg/m2/dose, days 1-84	18.75mg/m2/dose, days 1-14, 29-57	neutropenia
	PO Methotrexate	20mg/m2 weekly x12 weeks	5mg/m2, days 8, 50	
	IT Methotrexate	15mg, days 1, 29	7.5mg, days 1, 29	dose reduced for ommaya infusion
Maintenance				
Modified ANHL0131	Vincristine	1.5mg/m2/dose, days 1 q3weeks	0.525-0.9mg/m2/dose, d1	q3 monthly dosing interval
	Prednisone	20mg/m2 BID, days 1-5 q3 weeks	10mg/m2 BID, days 1-5	q3 monthly dosing due to adrenal insufficiency requiring hydrocortisone and thrush
	6MP	225mg/m2, days 1-3 q3 weeks	90mg/m2, days 1-5	prolonged neutropenia requiring neupogen to keep ANC >1000
	IV Methotrexate	20mg/m2/dose, ?	5-10mg/m2/dose, d1 q3 weeks	with leukovorin rescue
	IT Methotrexate	15mg, d1 of cycles 1-3	7.5mg q month x3 months	dose reduced for ommaya infusion

Cancer treatment

- Future directions
  - Artificial intelligence can optimize cancer drug discovery, development, and administration
  - Quadratic phenotypic optimization platform (QPOP) has been used to evaluate cancer combination therapies as well as dosages

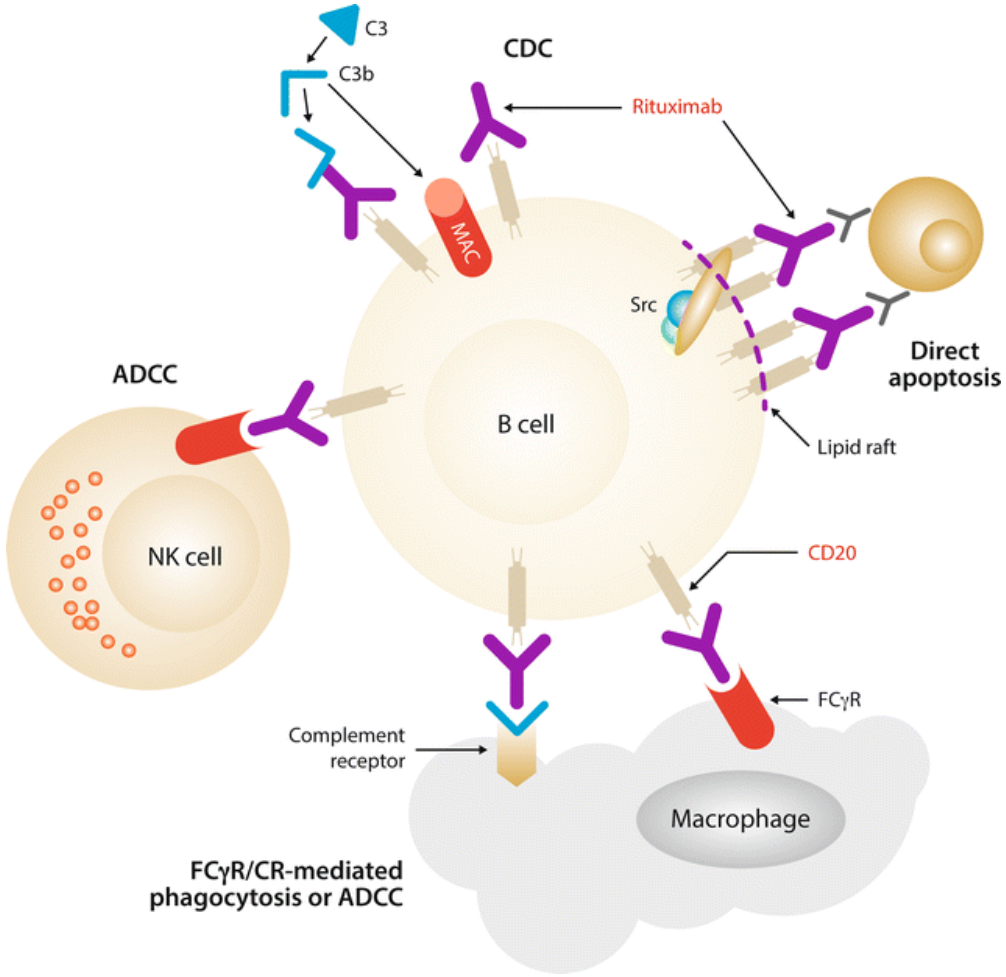




*Lee DK, ***Chang VY***, Kee T, Ho CM, Ho D. Optimizing Combination Therapy for Acute Lymphoblastic Leukemia Using a Phenotypic Personalized Medicine Digital Health Platform: Retrospective Optimization Individualizes Patient Regimens to Maximize Efficacy and Safety. *J Lab Autom.* 2016 Dec 5.

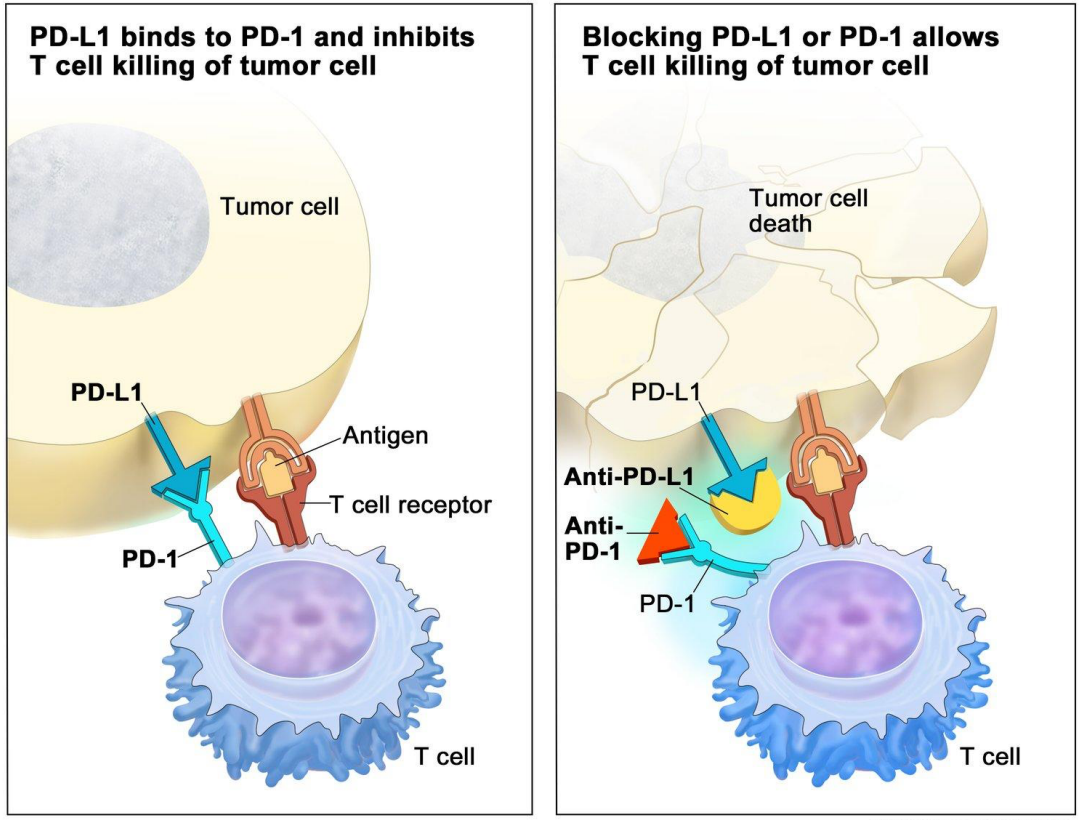
Cancer treatment

- Future directions
  - Targeted therapies are drugs that target specific genes or proteins that are involved in growth and survival of cancer cells
  - Monoclonal antibodies block a specific target on the outside of cancer cells or in the areas around cancer
  - Small molecule therapies are drugs that block cancer cells from growing and surviving



Cancer treatment

- Future directions
  - Immunotherapy helps the immune system fight cancer
  - Immune cells can be found in and around tumors (tumor-infiltrating lymphocytes or TILs)
  - Immune checkpoint inhibitors are drugs that block immune checkpoints
  - T-cell transfer therapy boosts natural ability of T cells to fight cancer
  - Treatment vaccines boost immune system to respond to cancer cells



Cancer prevention

- Modifiable lifestyle and environmental factors to reduce tumor risk
  - Avoidance of sun, alcohol
  - HPV and hepatitis B vaccine
  - Balanced nutrition
- Identifying pre-cancerous conditions
- Chemo-prevention
  - Large-scale chemical/drug screens to identify agents may reduce or eliminate cancer risk
  - Tamoxifen for breast cancer
  - Metformin in Li-Fraumeni Syndrome
  - NAD+ in Werner Syndrome
- Risk-reducing surgery

Reichrath J, Rass K. Ultraviolet damage, DNA repair and vitamin D in nonmelanoma skin cancer and in malignant melanoma: an update. Adv Exp Med Biol. 2014;810:208-233. doi:10.1007/978-1-4939-0437-2_12

Thank you!

- Bloom Syndrome Association
- Bloom Syndrome Registry
- All Bloom Syndrome patients and families!

- Ahmed Suleiman
- Rhys Brook

Questions/Discussion!

Mattel Children's Hospital UCLA