CUTANEOUS LYMPHOMA FOUNDATION

Overview of Cutaneous Lymphomas

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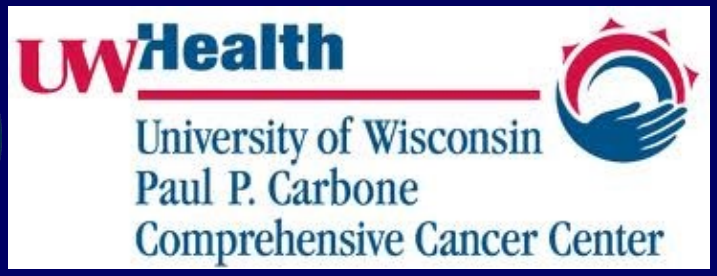
THE UNIVERSITY of WISCONSIN MADISON



UW Health

University of Wisconsin
Paul P. Carbone
Comprehensive Cancer Center

Morning Faculty Program

- Overview of Cutaneous Lymphoma
  Dr. Gary S. Wood (no conflicts of interest)
- Diagnosis & Staging of Cutaneous Lymphoma
  Dr. Keri Chaney
- Break
- Treatment of Early Stage Disease
  Dr. Bob Glinert
- Treatment of Later Stage Disease
  Dr. Stefan Schieke
- Q&A Panel
  All four MDs

Learning Objectives

- Basic immunology and skin biology
- Appearance and classification of skin lymphomas
- How lymphomas develop
- General aspects of treatment

What is a lymphoma?

A cancer of lymphocytes

What are lymphocytes?

White blood cells (T, B, NK) derived from the bone marrow that mature in the thymus, lymph nodes and spleen

What do lymphocytes normally do?

Adaptive Immunity: antigen-specific receptors

CD4+ T cells: help other immune cells

CD8+ T cells: kill foreign or abnormal cells

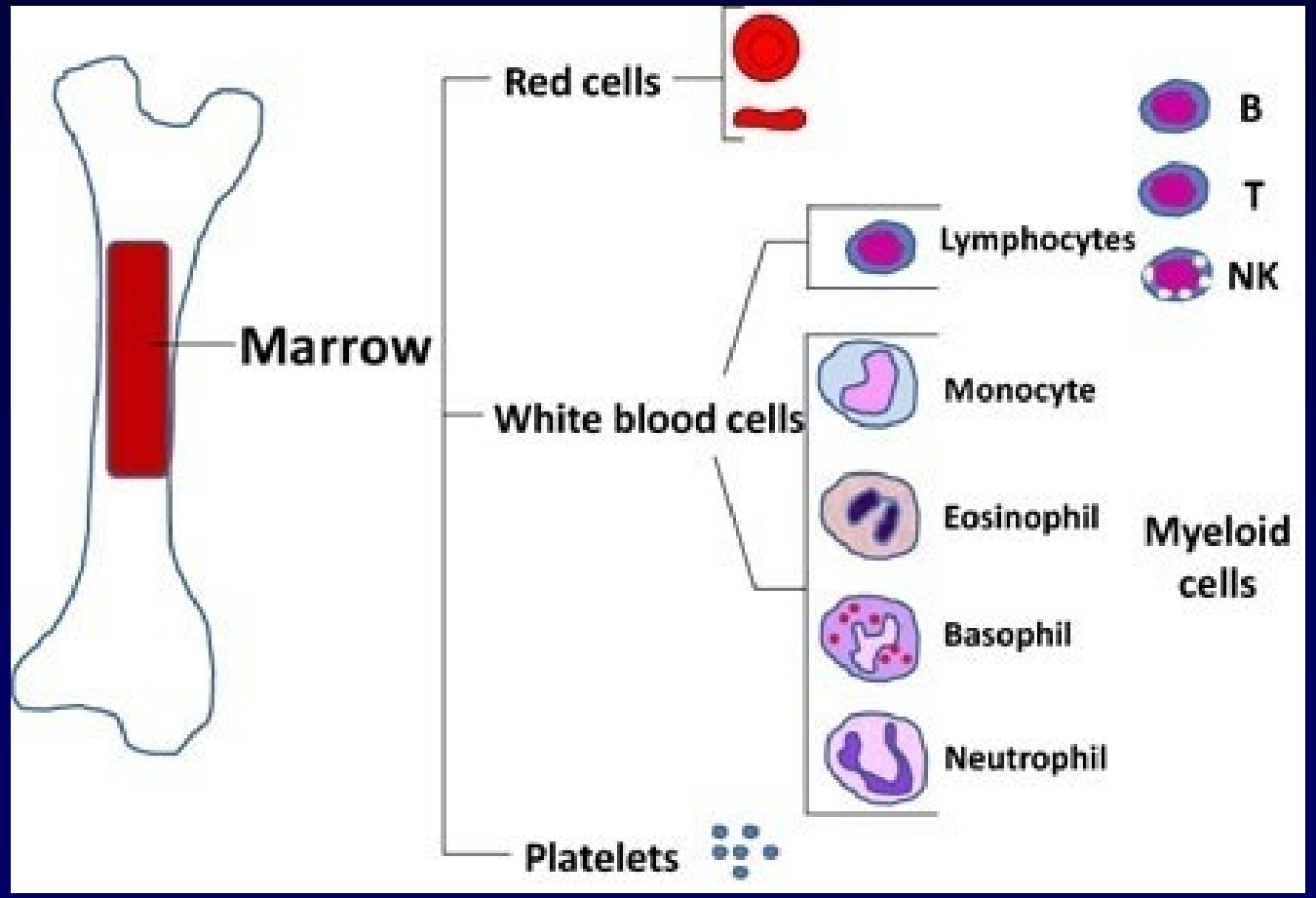
B cells: make antibodies

Innate Immunity: invariate receptors

NK cells: kill foreign or abnormal cells

(unlike CD8+ T cells, do not use an antigen-specific T cell receptor)

Origin of Lymphocytes

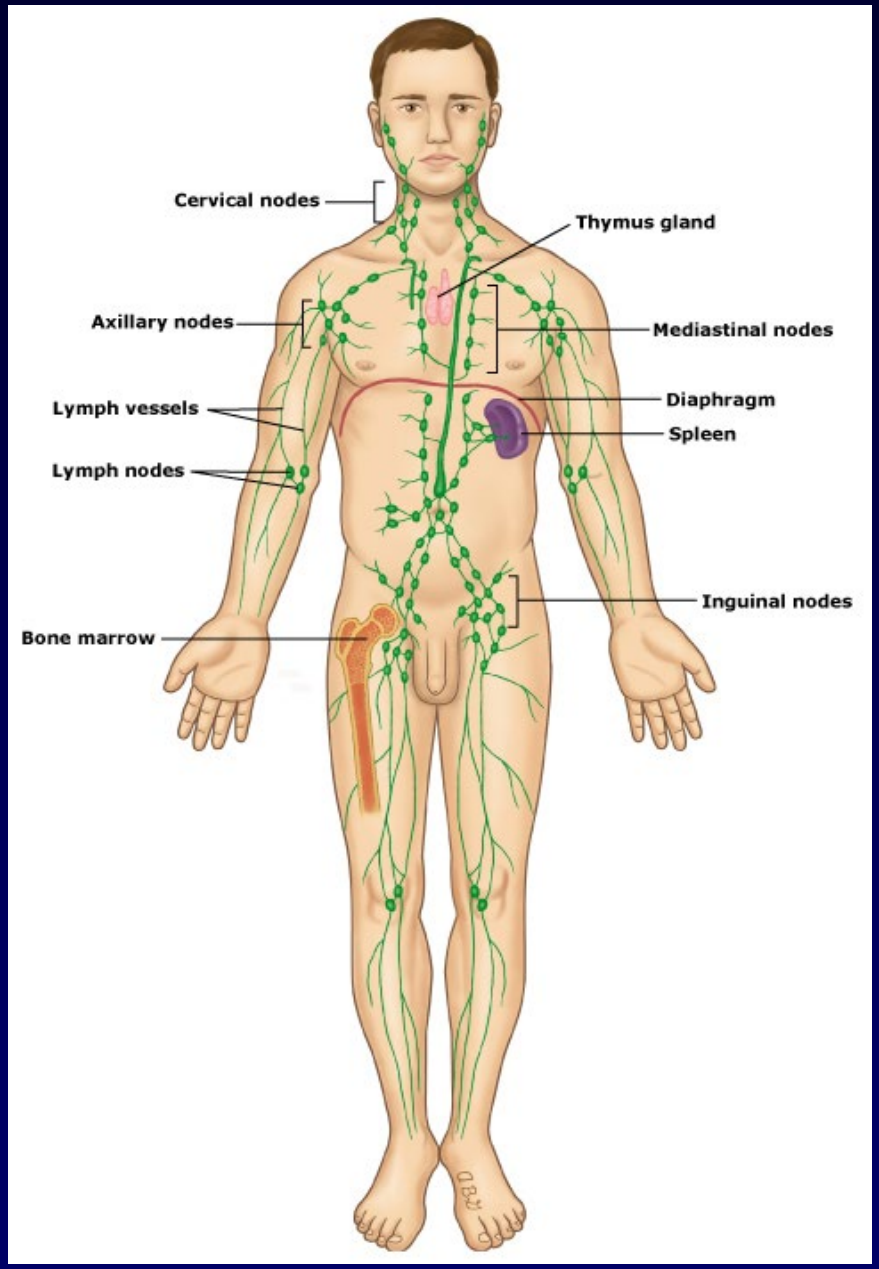


After forming in the bone marrow, lymphocytes mature in the thymus, lymph nodes and spleen.

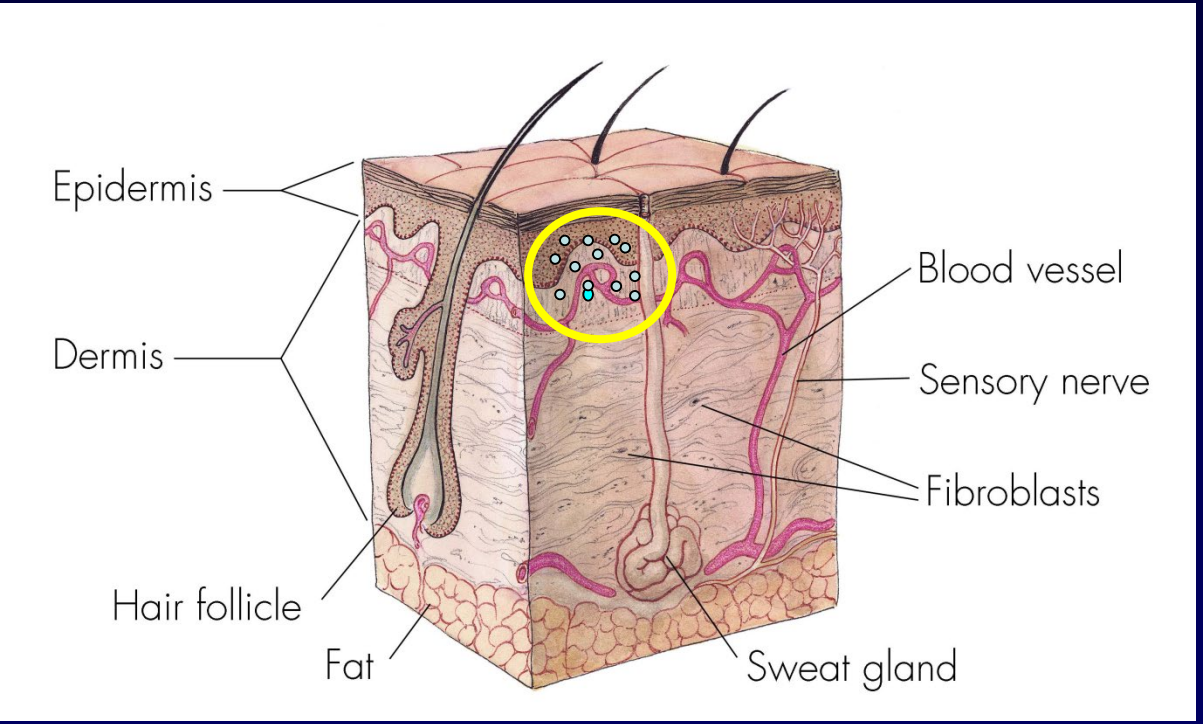
They circulate throughout the body tissues (including the skin) traveling via the blood and lymphatic vessels.

There are different subsets of T cells that home to specific tissues like the skin.

MF is a cancer of skin-homing T cells.



Skin Structure

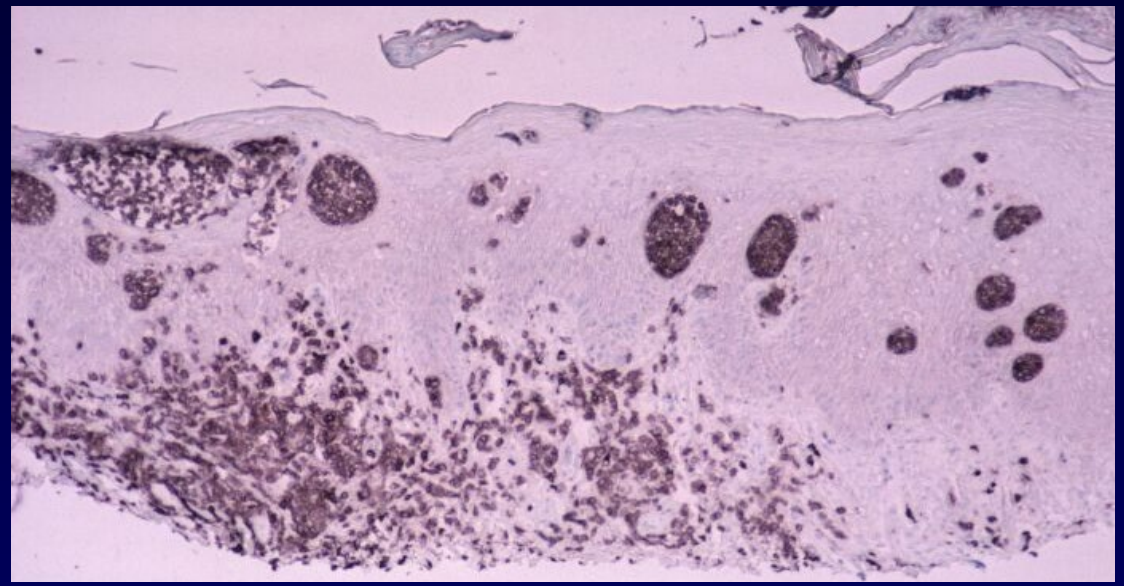


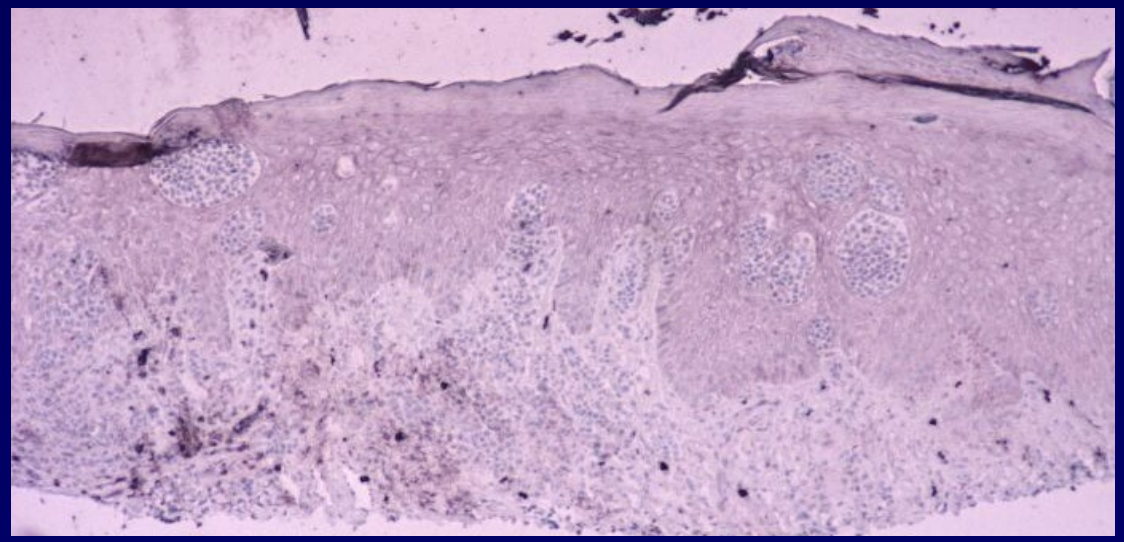
MF/SS

Other T- & B-Cell Lymphomas & Advanced MF/SS

Subcutaneous Panniculitic T-Cell Lymphomas & Advanced Lymphomas

Immunophenotype of MF/SS: Mature Memory SALT Helper T Cell





Mature Memory T Cell

TCR-ab, CD45RO

Deficiencies
CD3dim, CD7-, CD26-
(CD2, CD5)

Helper

CD4

MF: Effector Memory

CLA, CCR4

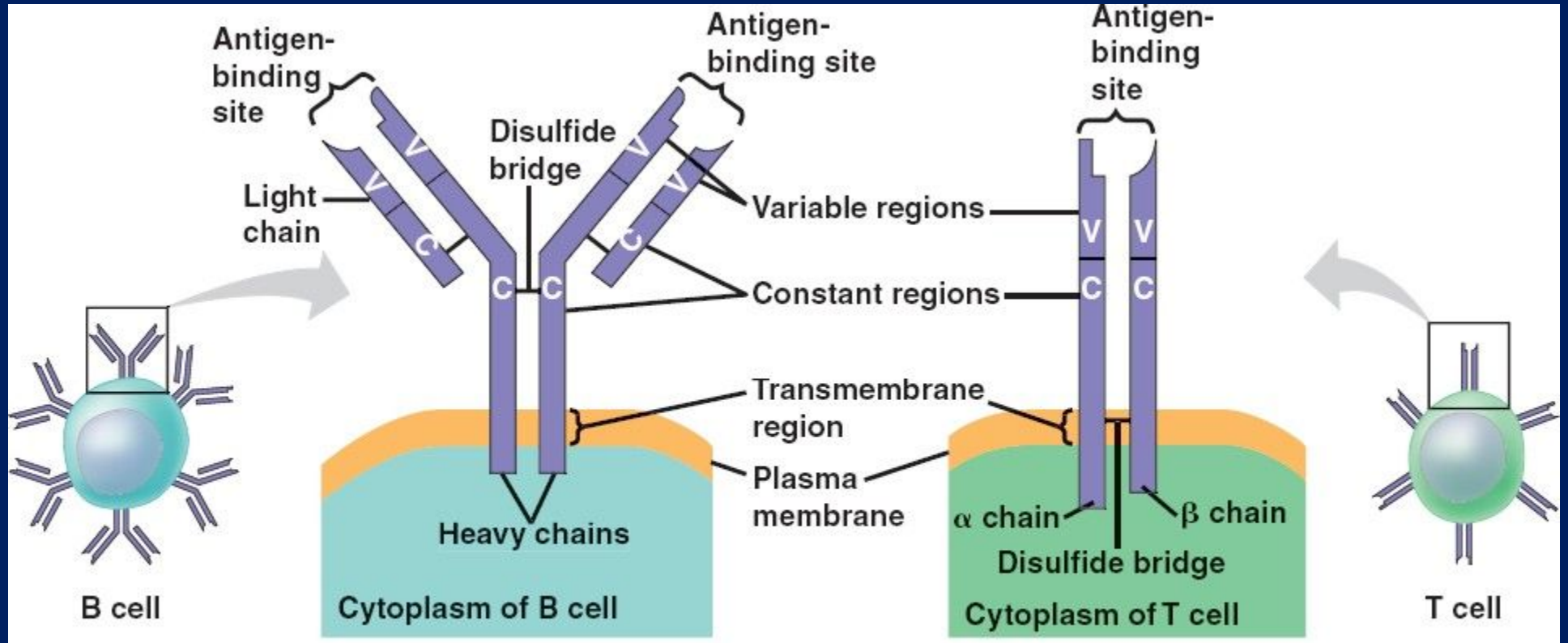
SS: Central Memory
CCR7/L-selectin

T-reg Inducible

CD25, CTLA4, FoxP3.

IL10, TGF-b

Clonality of T-Cell & B-Cell Lymphomas (the tumor's "fingerprint")



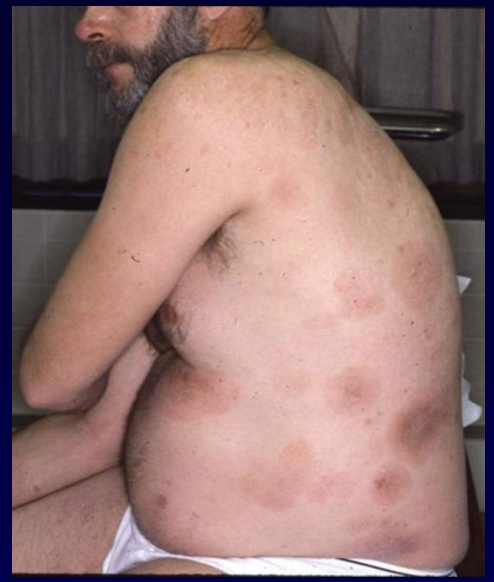
(a) A B cell receptor consists of two identical heavy chains and two identical light chains linked by several disulfide bridges.

(b) A T cell receptor consists of one α chain and one β chain linked by a disulfide bridge.

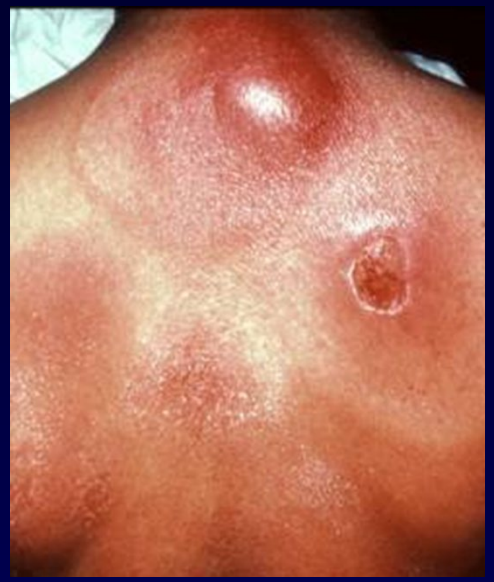
What do skin lymphomas look like?

MF and SS

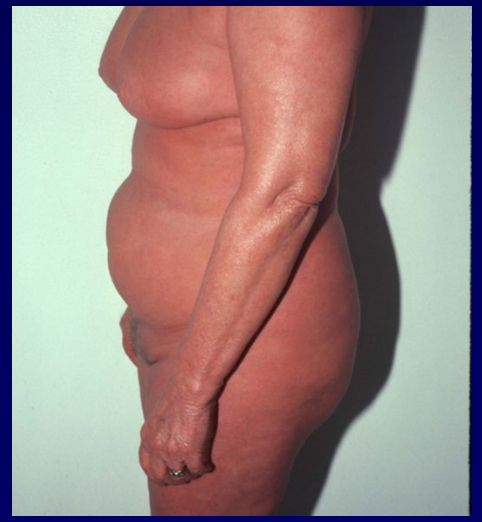
Patch/Plaque



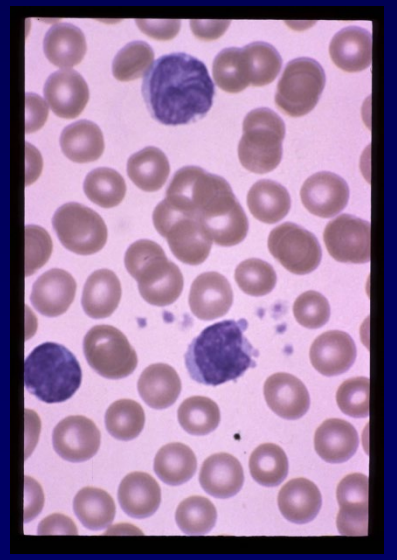
Tumor



Erythroderma



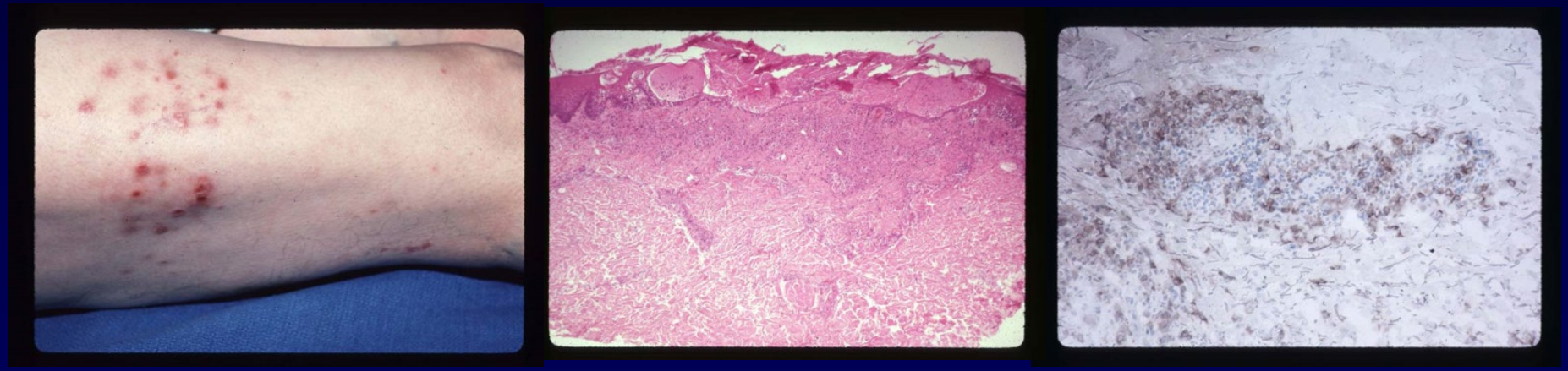
Sezary Cells



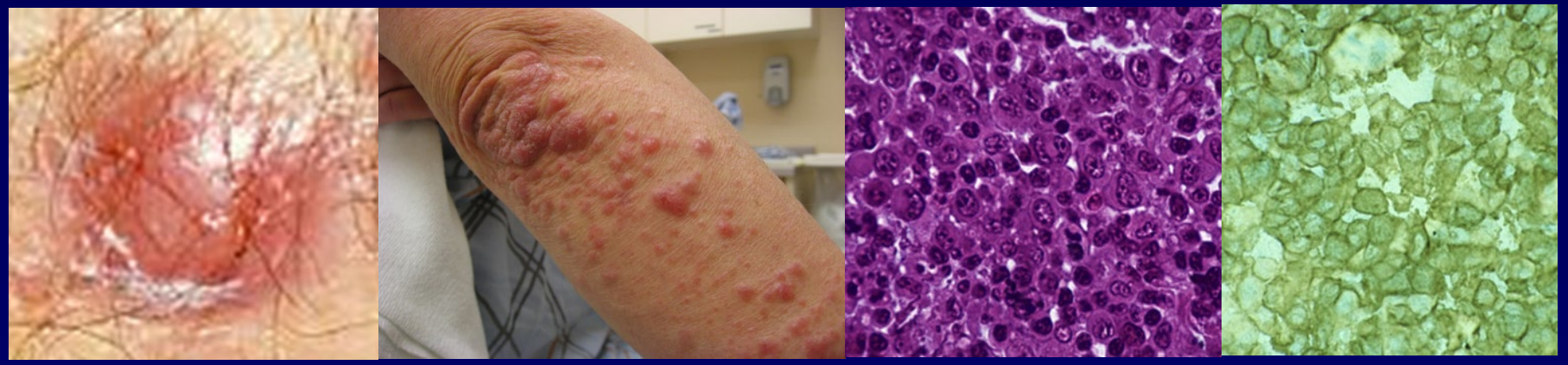
LyP and ALCL:

Two ends of a CD30+ CLPD spectrum that includes intermediate forms.

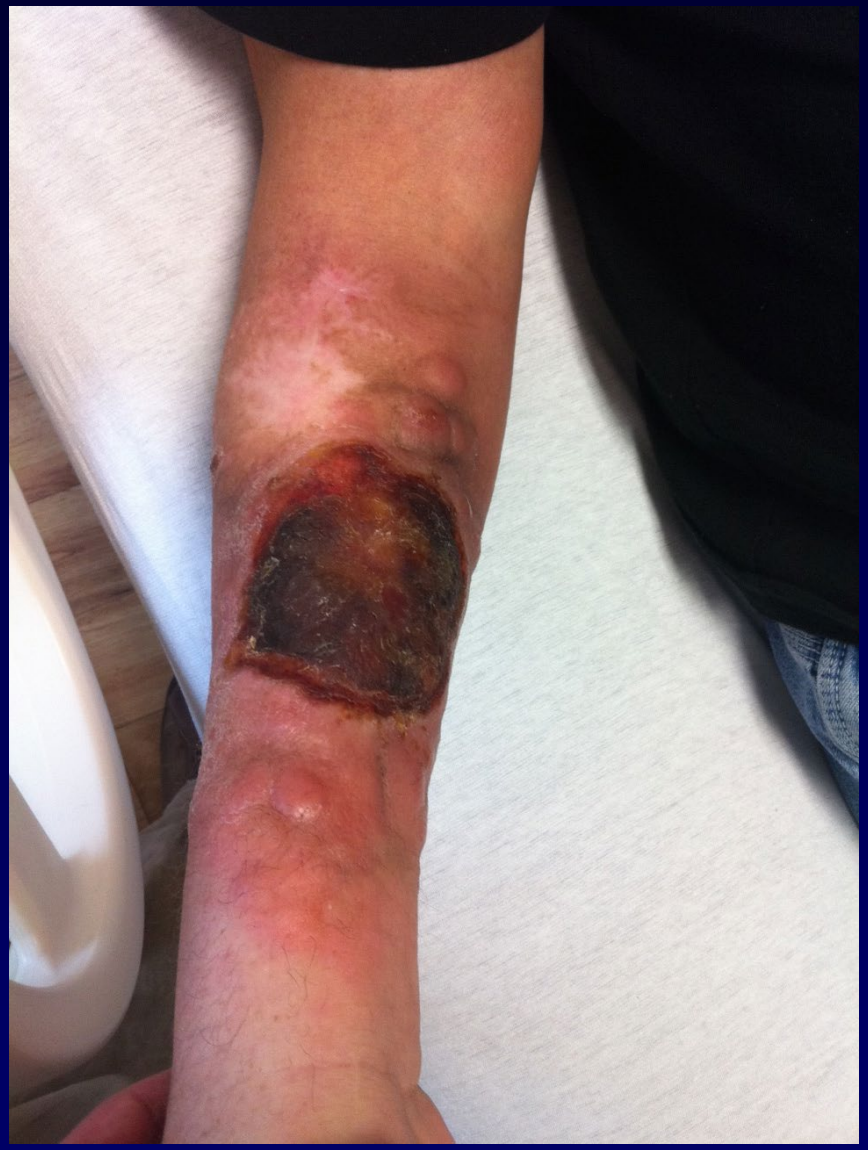
LyP



ALCL



Primary Cutaneous Aggressive Epidermotropic Cytotoxic T-Cell Lymphoma (Berti's)



How are skin lymphomas classified?

CutaneousT-Cell Lymphomas (75% of total)

Indolent (5 yr survival >75%)

- MF and variants
  (Hypopigmented, follicular, GSS)
- LyP-CD30+ ALCL
- Subcutaneous panniculitic alpha/beta TCR, (usually CD8+)
- Small/medium CD4+ T-cell LPD (Tfh)
- Acral CD8+ TCL

~5/6 of CTCLs; ~2/3 of skin lymphomas

Cutaneous T-Cell Lymphomas

Aggressive (5 yr survival <25%)

- SS
- NK/T, nasal type * CD56+ EBV+
- Aggressive epidermotropic CD8+ * (Berti's)
- Gamma/delta TCR * CD56+
- Hydroa vacciniforme T-cell LPD/mosquito bite rxn* EBV+
  (progress to systemic EBV+ T/NK lymphomas)
- Peripheral TCL, unspecified (large CD4+ pleomorphic)
- Adult T cell leukemia/lymphoma (classic type) HTLV-1+

* ulcerative

- (CD4+CD56+CD123+ blastic plasmacytoid DC neoplasm)
  "hematodermic lymphoma"

Cutaneous B-Cell Lymphomas (25% of total)

Indolent (5 yr survival >95%)

- Marginal zone (immunocytoma) bcl 2+6-
  two types (-/+ IgM/CXCR3)
- Follicle center cell bcl 2-6+*
- Mucocutaneous ulcer EBV+

Intermediate (5 yr survival 50-70%)

- LCL, leg-type bcl 2+6+, cIgM+, 50% cIgD+ MUM-1/IRF4+, FoxP1+, often MYC+/MYD88+
- LCL, intravascular & other

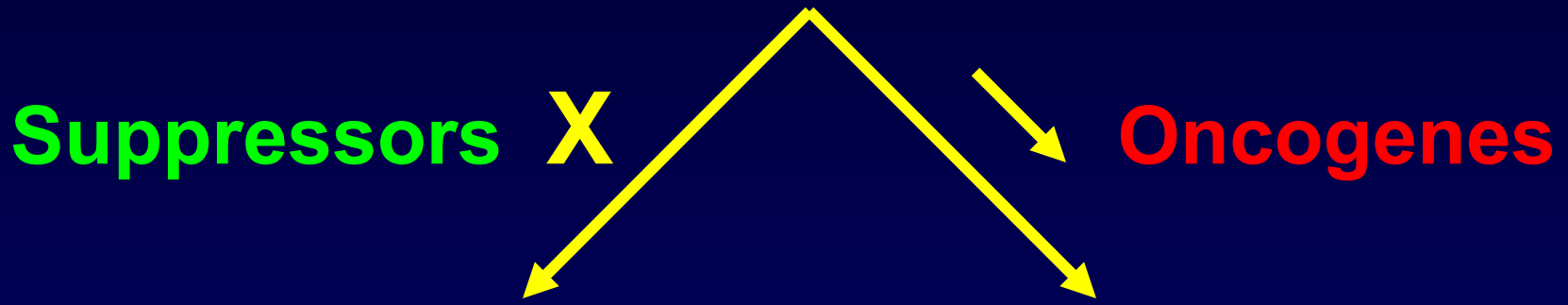
* prognosis intermediate if on leg, MUM-1+ or FoxP1+

What causes lymphomas?

- Combinations of inflammation, infection & mutations.
- Factors that stimulate cell growth, inhibit cell death and select for the heartiest members of the herd.
- Selective growth leads to emergence of dominant tumor clones identified by identical antigen receptors (T-cell receptor or B-cell receptor).

Lymphomagenesis

Normal T or B Cell



↓ Apoptosis → ↑ Proliferation

Lymphoaccumulative Disorder

Lymphoproliferative Disorder

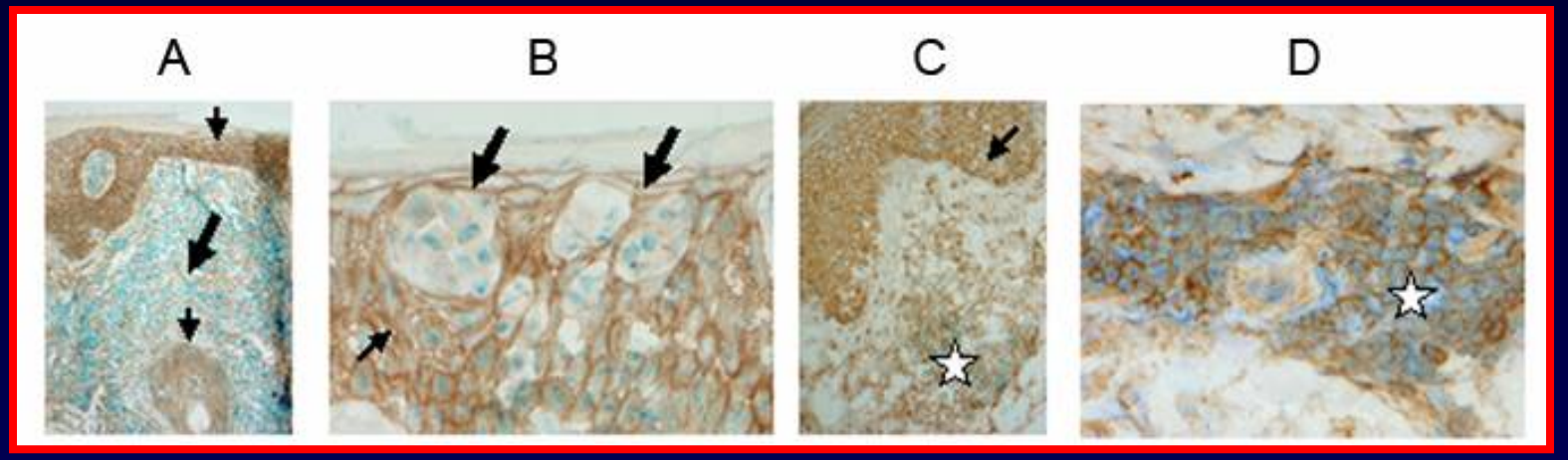
Apoptosis = programmed cell death, often activation-induced cell death (AICD)

FAS Apoptosis Pathway Expression in MF

JID 2009

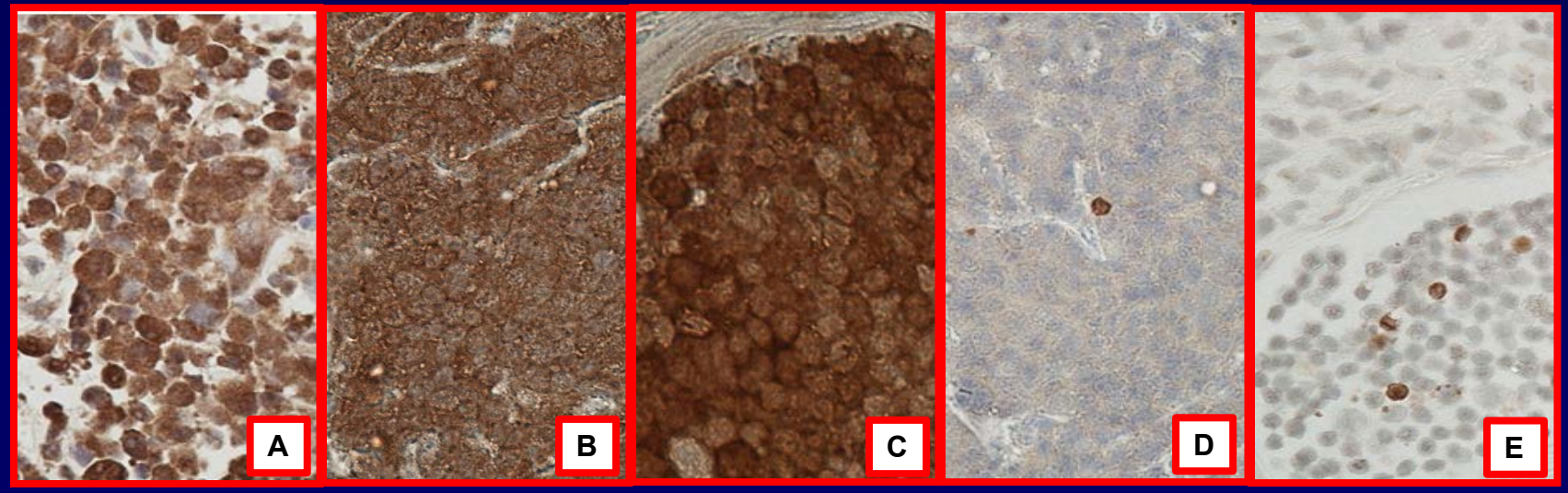
FAS: MF (A,B)

FAS: Dermatitis (C,D)



JAAD 2012

FADD (A), uncleaved Caspase 8 (B), uncleaved Caspase 3 (C), cleaved Caspase 8 (D) and cleaved Caspase 3 (E)



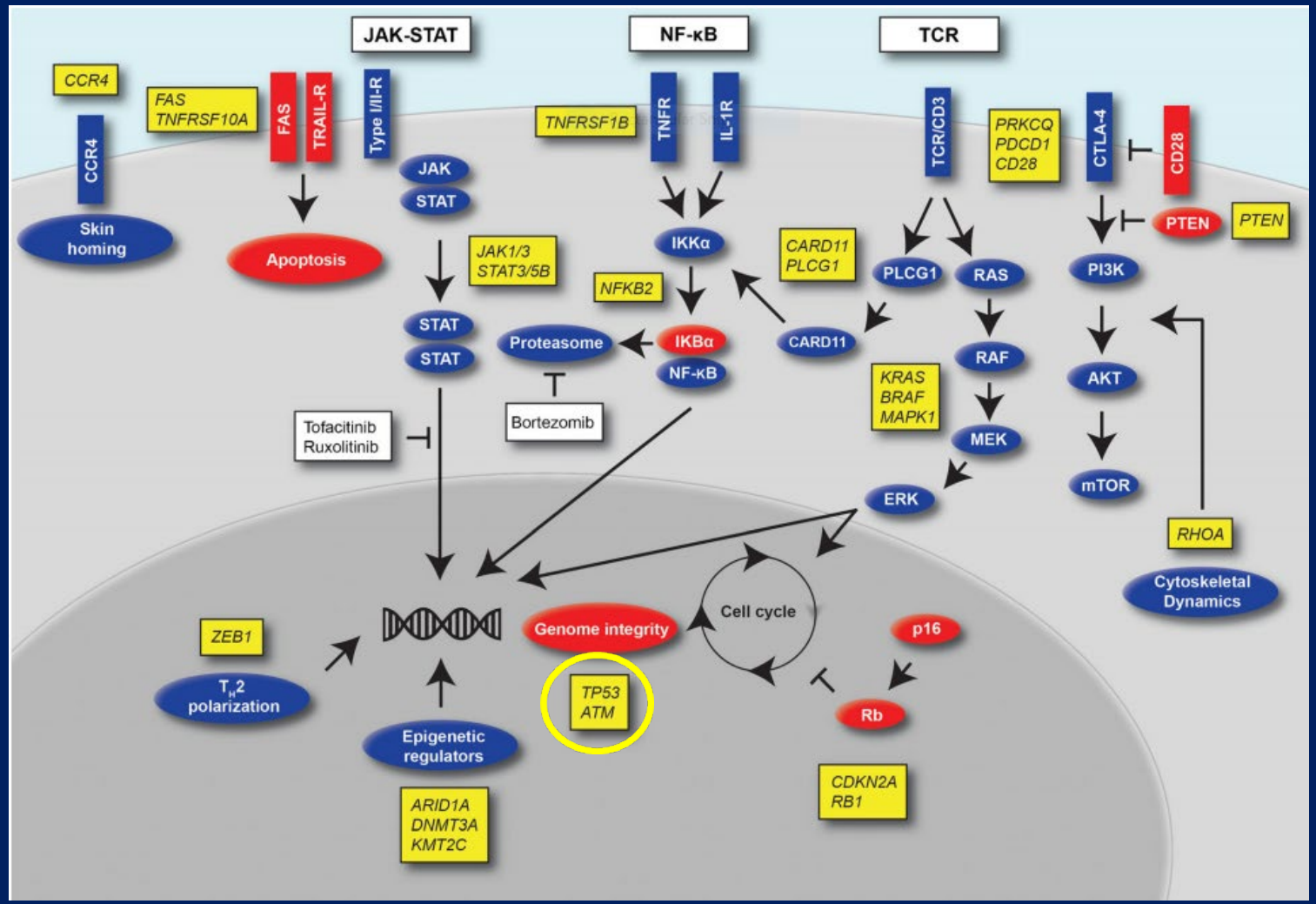
Common Mutations in Advanced MF/SS

Average: 12/case; clonal; TP53 in 92%
Most mutations are SCNVs

Apoptosis: FAS, DR4
JAK/STAT: JAK1,3, Stat 3, 5B
NFkB: TNFR2, NFkB2, TNFAIP3
TCR: PLCg1, CARD11, PKCϴ, PD1, CD28
Homing/Differentiation: CCR4, ZEB1
MAPK: KRAS, BRAF, MAPK1
PI3K/AKT: PTEN, RHOA
Epigenetic: DNMT3A, ARID1A, KMT2C, CTCF
Cell Cycle: CDKN2A, RB, MYC, IRF4
Genome Integrity: **TP53**, ATM

Enhanced genes: amplification, mutation
Suppressed genes: deletion, mutation

Key Questions Still Unanswered:
How do mutations evolve over time?
How do mutations vary among cells?



Ref: Choi, 2016

Rx Strategy Based on Lymphoma Biology

- Control itch, infection and “infrastructure” (nutrition, exercise, sleep, mindfulness)
- Indolent disease can often be controlled by conservative skin-directed Rx with low toxicity
- Multiple mutations → Rx resistance
- Aggressive disease requires more toxic Rx: Combination Rx > Sequential Rx > Mono Rx (less chance for Rx-resistant mutations)

Wood Lab:
Novel Rx that kills faster by boosting apoptosis and slowing tumor growth

MTX/NBUVB Derm Clinics 2015

Gentian Violet JAMA Derm 2018
(also kills bacteria and fungi)
(killing Staph reduces MF tumor clone in skin)
Lindahl Blood 2019

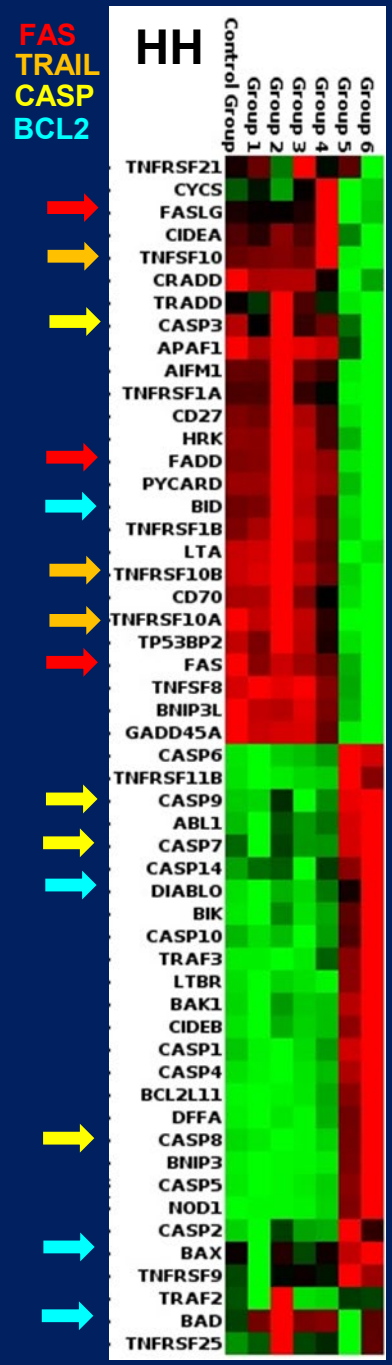
MTX/PDT Photochem/biol 2015, 2018

MTX/Fedratinib/Resveratrol JID 2019
(also inhibits JAK/STAT)

BETi/HDACi Neoplasia 2019
(birabresib/romidepsin, epigenetic agents)

BETi/HDACi:

3 waves of apoptotic factors at 6, 48 and 96 hrs. Up to 90% kill of CTCL cells *in vitro* and *ex vivo* by 4 days.



Other Novel Rx in Development

- ^{90}Y-NM600 (systemic RT; Hernandez Comm Biol 2019)
- BETi (miR-214 inhibitor; Kohnken JID, 2019)
- ABT-199 & dimethyl fumarate (Bcl-2 & NFkB inhibitors; Froehlich Blood, 2019)

SUMMARY

- Cutaneous lymphomas are tumors of white blood cells that home to the skin
- CTCLs are more common than CBCLs
- MF and CD30+ disorders (LyP and ALCL) are the most common CTCLs and most cases are indolent
- Most CBCLs are indolent
- Indolent cases can be treated with low toxicity RX
- Aggressive cases require more toxic RX
- Combination RX often works better than single agent RX

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- **Break**
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Thank You!