Riposta immune versus stato immune

Russell E. Lewis
U.O. Malattie Infettive,
Policlinico S. Orsola-Malpighi
Dipartimento di Scienze Mediche e Chirurgiche
Alma Mater Studiorum Università di Bologna

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

"Immunodeficiency" is a heterogeneous concept

IDSA 2013 Guidelines for Vaccination of the Immunocompromised Host- Definition of "high-level" immunosuppression

- Combined primary immunodeficiency disorder
- Receiving cancer chemotherapy
- Within 2 months of solid organ transplantation
- Hematopoietic stem cell transplantation (transplant type, donor, stem cell source, GVHD and treatment)

Rubin LG, Levin MJ, Ljungman P, et al. *Clin Infect Dis.* 2014;58(3):309-318.

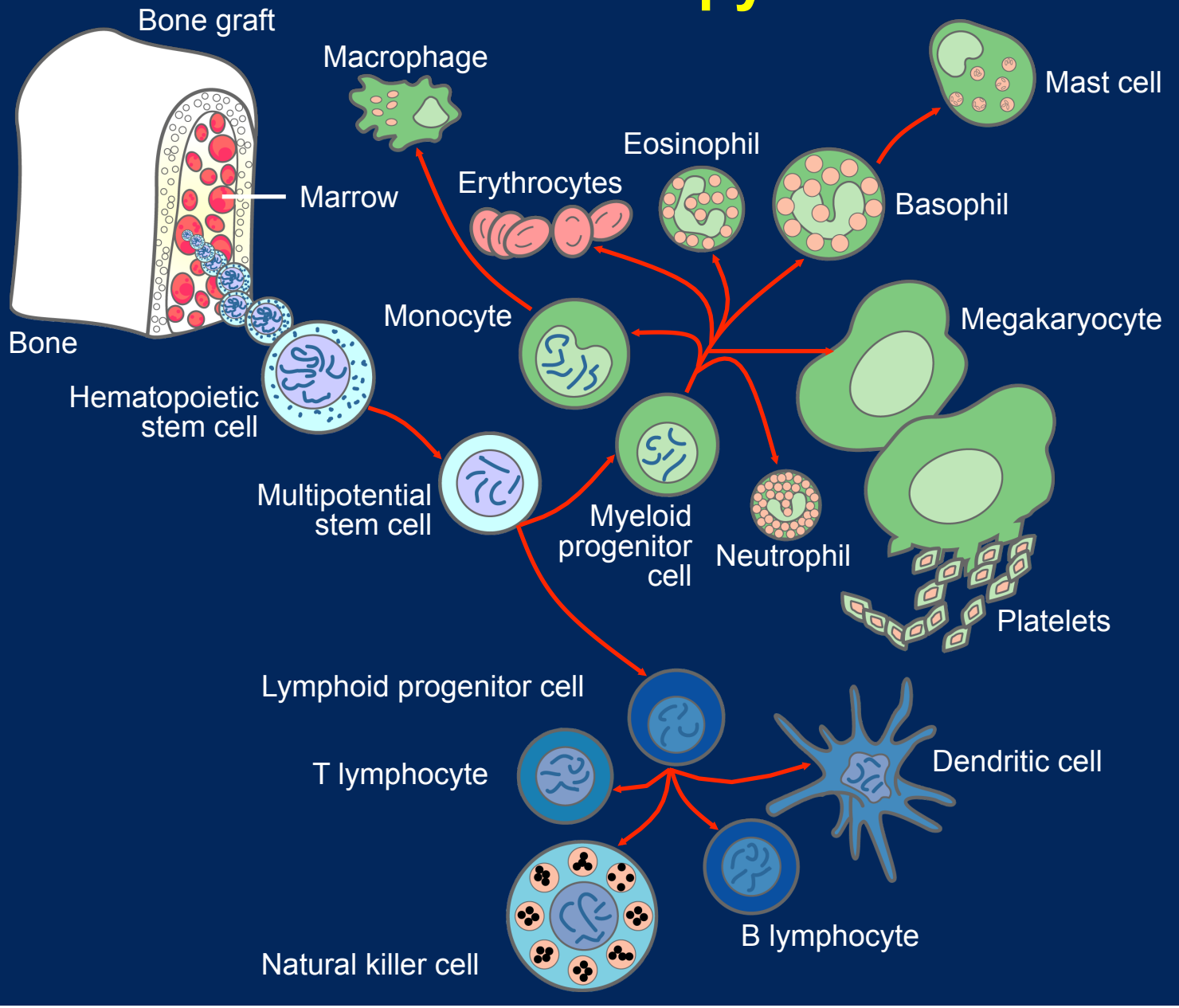
"Immunodeficiency" is a heterogeneous concept

IDSA 2013 Guidelines for Vaccination of the Immunocompromised Host- Definition of "high-level" immunosuppression

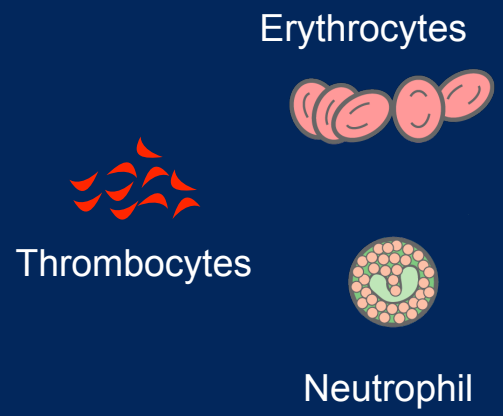
- HIV infection with $CD4^+$ T-lymphocyte count <200 cells/ mm3 for adults
- Daily corticosteroid therapy with a dose ≥ 20 mg of prednisone equivalent for ≥ 14 days
- Receiving biologic immune modulators, i.e. TNF-α inhibitor, alemtuzumab or rituximab

Rubin LG, Levin MJ, Ljungman P, et al. *Clin Infect Dis.* 2014;58(3):309-318.

Immediate and long-term effects of chemotherapy



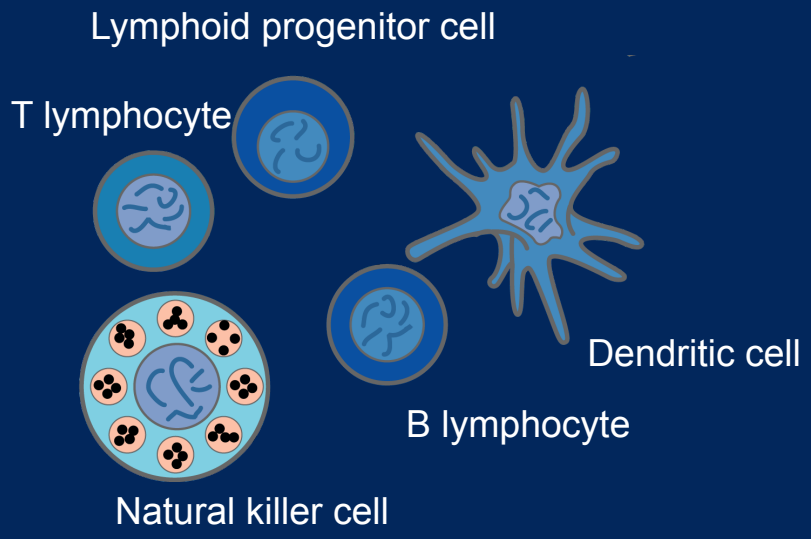
Depletion of RBCs, leukocytes and platelets



- **Short lived, post-mitotic, terminally differentiated**
- **Continuously replenished via repetitive cycles of hematopoietic stem cell differentiation**
- **Complete repopulation after 14-21 days of cytotoxic antineoplastic chemotherapy**

Mackall C. *Stem Cell* 2000,18:10-18

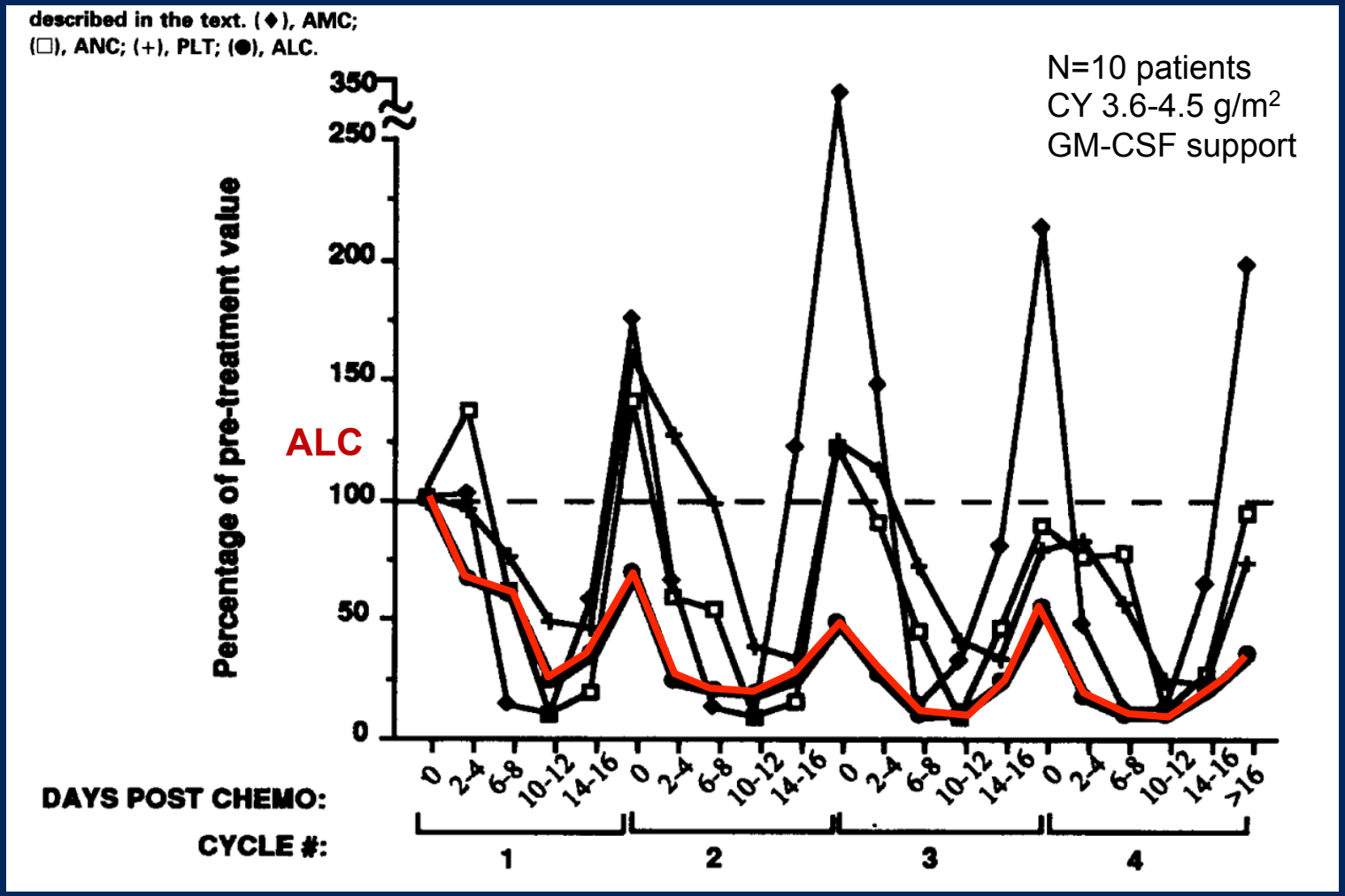
Lymphocyte depletion



- **Heterogenous group of short (effector, memory) and long-lived (naïve) cells**
- **Capable of substantial mitotic expansion**
- **Restoration of heterogenous populations and T- cell immunocompetence is slow and often incomplete**

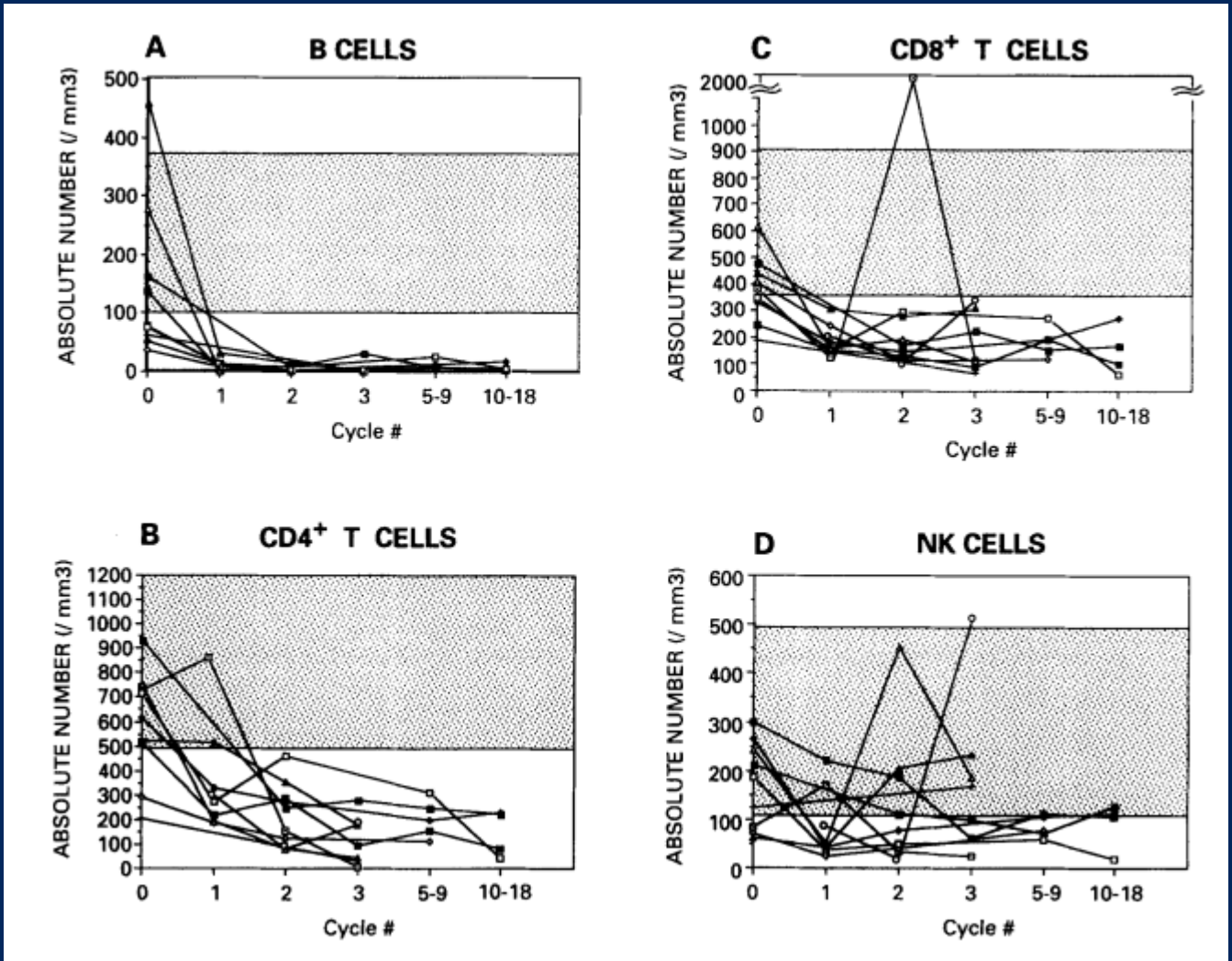
Mackall C. *Stem Cell* 2000,18:10-18

Impact of HD cyclophosphamide on T- cell dysfunction



Mackall C. *Blood* 1994;84:2221-2228.

Impact of HD cyclophosphamide on T- cell dysfunction



Mackall C. *Blood* 1994;84:2221-2228.

Lymphocyte depletion with purine analogues

(Fludarabine, 2-CdA, Pentostatin, Clofarabine)

- Prolonged decrease in CD4+
- Decrease in B cells
- Transient monocytopenia
- Transient NK cell reduction
- Variable effects on lymphocyte and NK cell function
- Variable effects on immunoglobulin levels

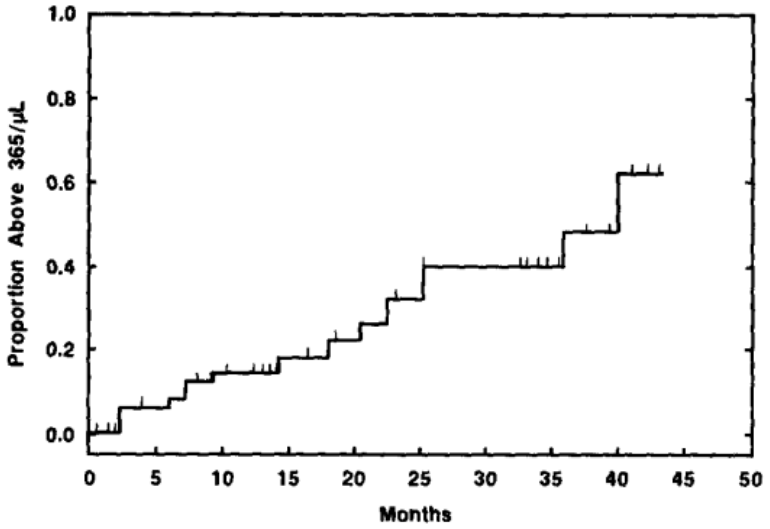
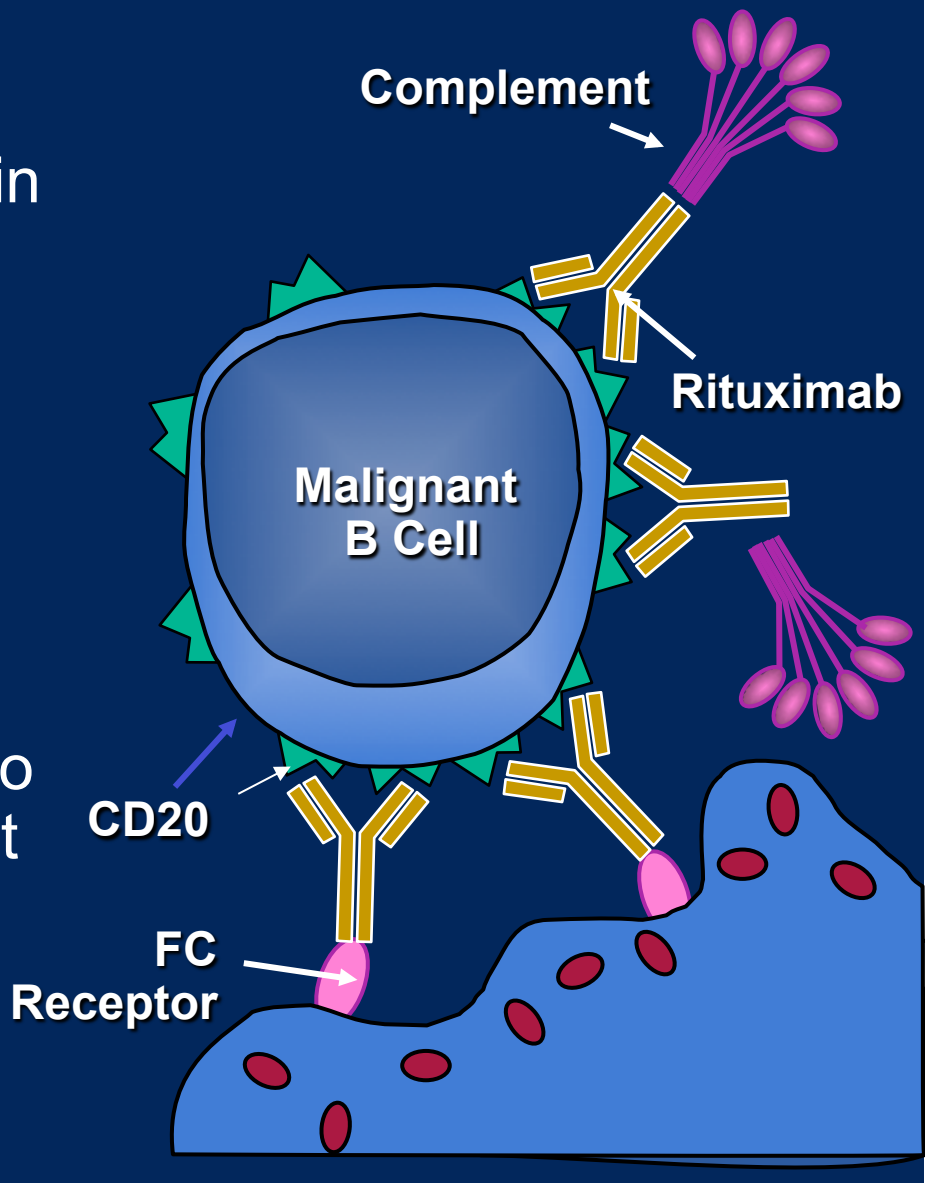


Fig 2. Time to achieve an absolute $CD4^+$ lymphocyte count of 365/μL after 2-CdA.

Seymour et al. Blood 1994 83:2906-2911
Cheson B. J Clin Oncol 1995;13:2431-2448.

Rituxan (Rituximab)

- Results in a 90% reduction in peripheral B-lymphocyte counts in 3 days
  - Recovery occurs slowly over 9-12 months
- Despite B-cell depletion, minimal decrease in serum immunoglobulin levels in most cancer patients, and no effect on serum complement



Rituximab blocks protective serologic response to influenza A (H1N1) 2009 vaccination in lymphoma patients during or within 6 months after treatment

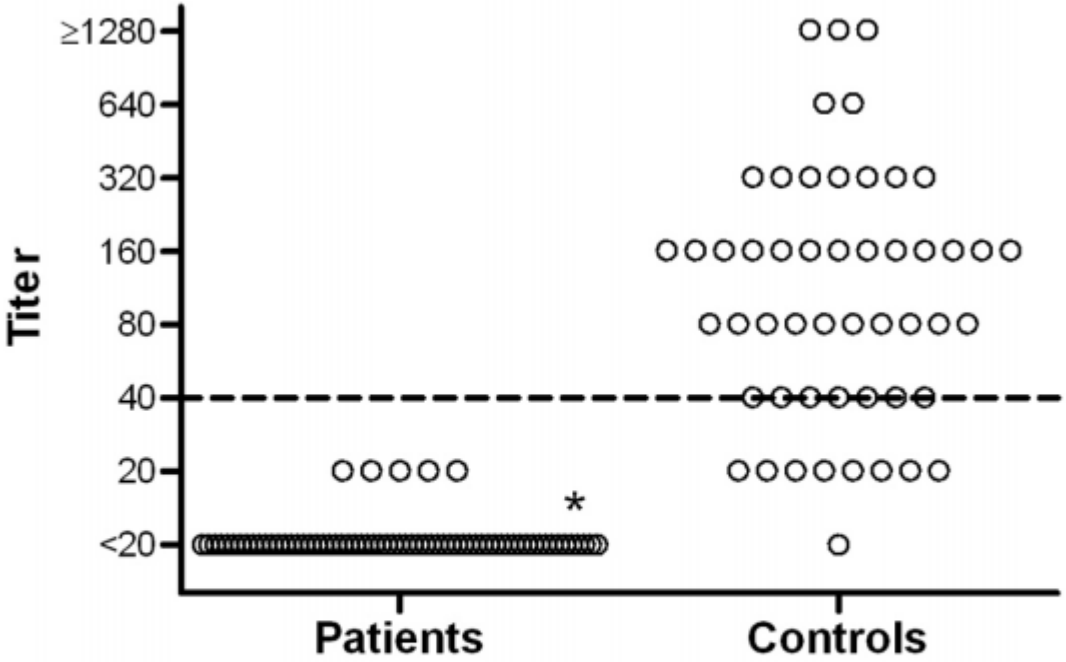


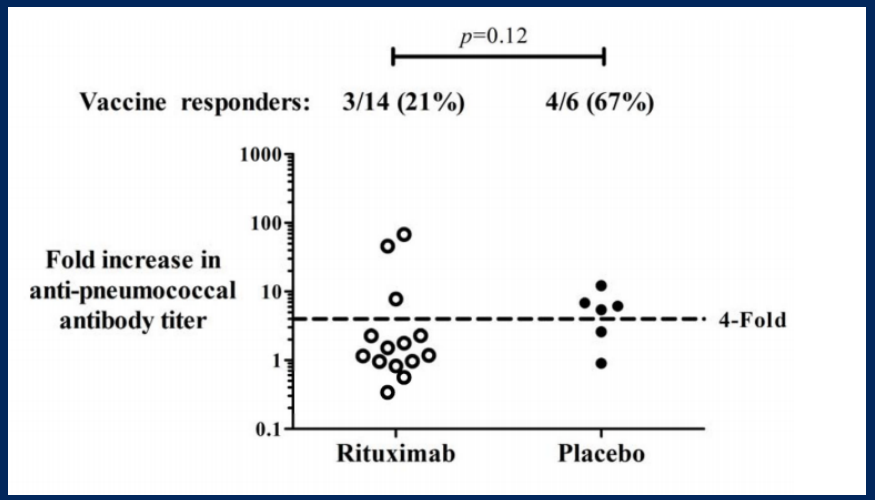
Figure 1. Postvaccination antibody titers in patients and controls. Titers are given as the reciprocal value of the highest dilution inhibiting the hemagglutination reaction. The dotted line indicates the protective antibody level of 40. *A total of 62 patients had an undetectable postvaccination titer.

Yri et al. Blood 2011;118:6769.

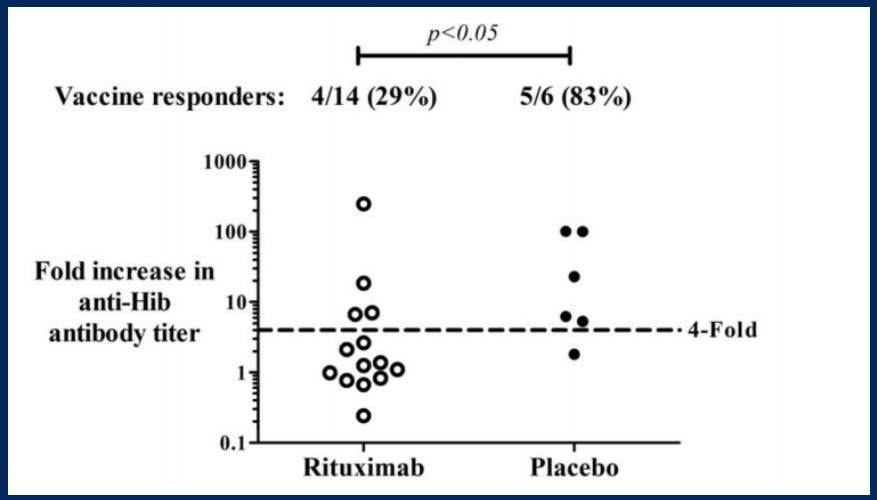
The effect of rituximab on vaccine responses in patients with immune thrombocytopenia

Subset of non-splenectomized patients randomized to rituximab or placebo + standard treatment (during prednisone taper)

T-cell independent vaccine



T-cell dependent vaccine



After treatment with rituximab, immunological responses to both polysaccharide and conjugated vaccines are impaired in patients with ITP

Splenectomized patients who have received rituximab may be at increased risk of infection because of compromised immune responses to vaccines.

Nazi et al. Blood. 2013 122(11): 1946–1953

Allogeneic HSCT: Phases of predictable immunosuppression

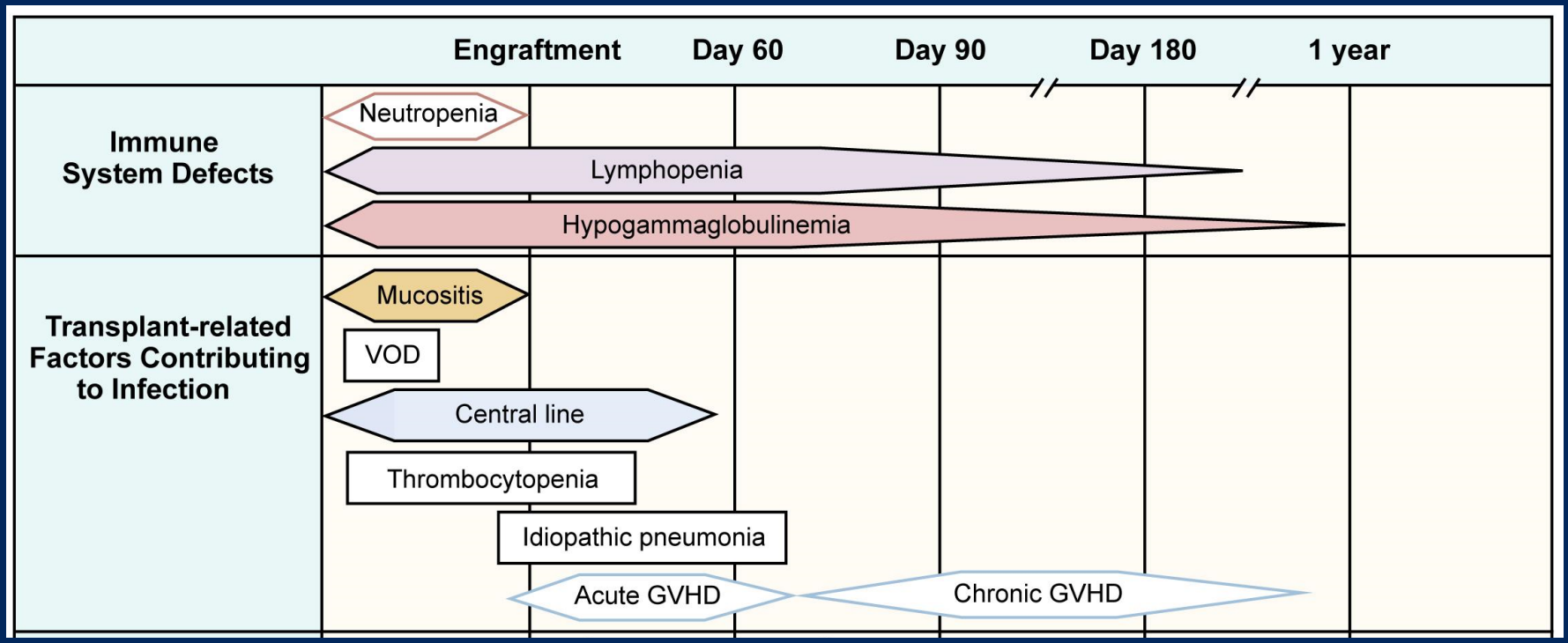
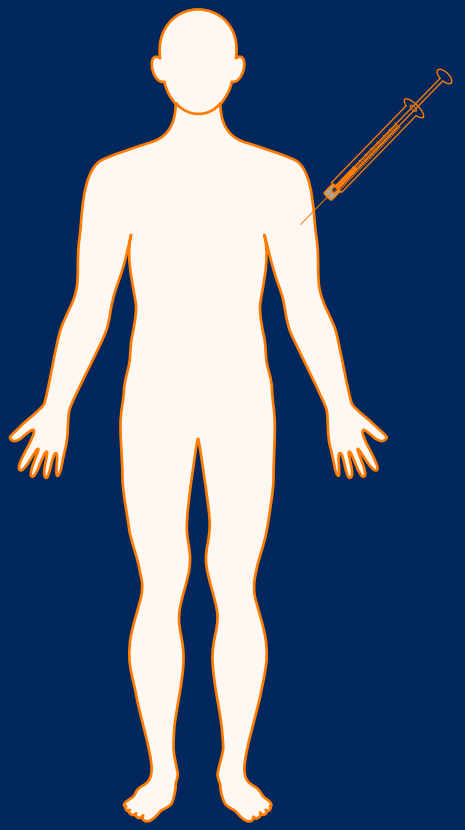


Image: National Cancer Institute. www.cancer.gov

Empiric vaccination considerations in patients with hematological malignancies



Consider vaccination ≥ 2 weeks before chemotherapy; but live-virus vaccines should be avoided in patients with active diseaseor ≥ 4 weeks of starting chemotherapy

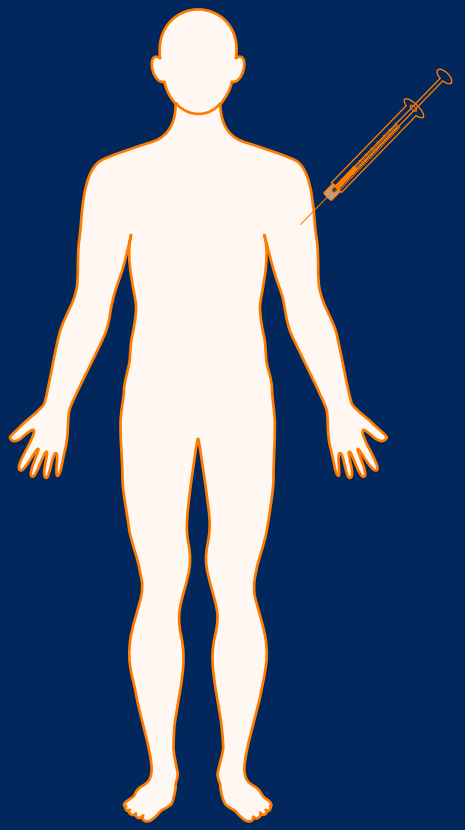
Inactivated vaccines are safe after chemotherapy, but response may be poor

Rituximab will suppress response to vaccination for 6-12 months

Avoid live-virus vaccines no earlier than 3 months after completing chemotherapy; 12 months after rituximab

Tsigrelis and Ljungman. Blood Reviews 2016;30:139-147.

Empiric vaccination considerations in patients undergoing allogeneic HSCT



Inactivated vaccines recommended if Interval before immunosuppression is ≥ 2 weeks (PCV, influenzae).

Adequate response to inactivated vaccines may develop as early as 3-6 months

Avoid live-virus vaccines ≥ 4 weeks before HSCT, and ≥ 24 months after HSCT if patient Is not immunosuppressed, seronegative, and No ongoing GVHD

Donor vaccination followed by early recipient vaccination may improve immune response post-HSCT (*H. influenzae, tetanus).*

Tsigrelis and Ljungman. Blood Reviews 2016;30:139-147.
Storek et al. Bone Marrow Transplantation (2004) **33,** 337–346

Safety and immunogenicity of heat-treated inactivated zoster vaccine (ZV_{HT}) in immunocompromised adults

Treatment Group	n[a]	Estimated GMFR[b]	90% CI	*P* Value
VZV-specific T-cell function by IFN-γ ELISPOT				
STM	56	3.0	(2.0, 4.6)	<.0001
HM	60	2.2	(1.4, 3.5)	.004
HIV-infected	60	1.8	(1.2, 2.7)	.026
Autologous HCT	38	9.0	(4.4, 18.4)	Exploratory only
Allogeneic HCT	40	0.2	(0.1, 0.4)	Exploratory only
VZV antibody response by gpELISA				
STM	55	2.4	(1.8, 3.0)	<.0001
HM	59	1.3	(1.1, 1.5)	.003
HIV-infected	60	1.4	(1.1, 1.7)	.017
Autologous HCT	38	0.9	(0.6, 1.3)	Exploratory only
Allogeneic HCT	36	1.0	(0.7, 1.4)	Exploratory only

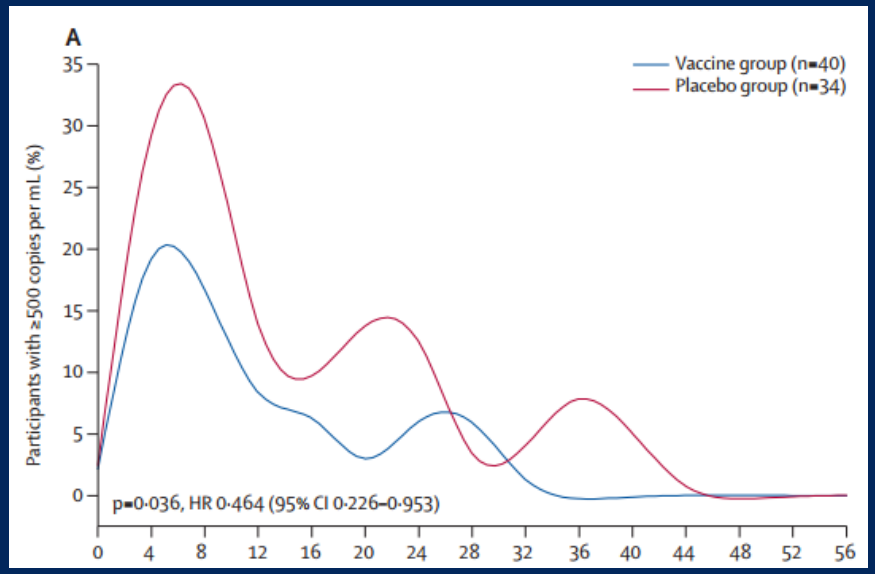
Abbreviations: CI, confidence interval; ELISPOT, enzyme-linked immunospot; GMFR, geometric mean fold rises; gpELISA, glycoprotein enzyme-linked immunosorbent assay; HCT, hematopoietic stem-cell transplant; HIV, human immunodeficiency virus; HM, hematologic malignancy; IFN-γ, interferon γ; STM, solid tumor malignancy; VZV, Varicella zoster virus.

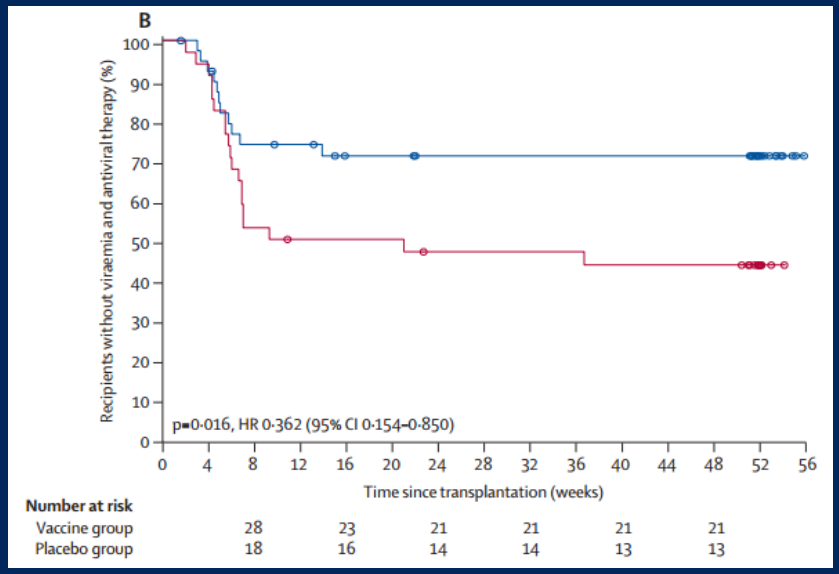
[a] n, no. of patients contributing to analysis (valid results at baseline or time points post-baseline).

ZVHT was generally safe and immunogenic through 28 days post-dose 4 in adults with STM, HM, and HIV. Autologous-HCT but not allogeneic-HCT patients had a rise in T-cell response; antibody responses were not increased in either HCT population.

Mullane et al. Journal of Infectious Diseases 2013;208:1375–85

New paradigms for viral control? CMV DNA vaccine in allo-HSCT





50% reduction in CMV viremia

Kharfan-Dabaja. Lancet Infect Dis 2012; 12: 290–99

Serologic testing to guide vaccination after intensive chemotherapy?

- **Serologic testing pre-and post-dosing for vaccine-preventable diseases with recognized serologic correlates of protection:**
  - **Diptheria toxoid**
  - **Hib**
  - **HepA**
  - **HepB***
  - **IPV**
  - **Rubella**
  - **Influenza**
  - **Measles***
  - **Tetanus toxoid**
  - **Varicella***
  - **Pneumococcal polysaccharide vaccines***

*immunogens that are less likely to induce reliable immune response

Rubin LG, Levin MJ, Ljungman P, et al. *Clin Infect Dis.* 2014;58(3):309-318.

Alternative approaches

- $CD4^+$ >200 mm^3 and/or
- Documented serological response to ≥ 1 vaccine

Rubin LG, Levin MJ, Ljungman P, et al. *Clin Infect Dis.* 2014;58(3):309-318.

Limitations of serologic testing

- Serum antibody concentration that correlates with protection is unknown for many pathogens
- Asplenic patients require higher antibody concentrations for protection against *S. pneumoniae* and *H. influenzae*
- Most assays do not report functional activity of antibodies (i.e. avidity)
- For zoster prevention, cell mediate immunity (CMI) is more predictive than antibodies

Rubin LG, Levin MJ, Ljungman P, et al. *Clin Infect Dis.* 2014;58(3):309-318.

Carter cancer-free following immune treatment

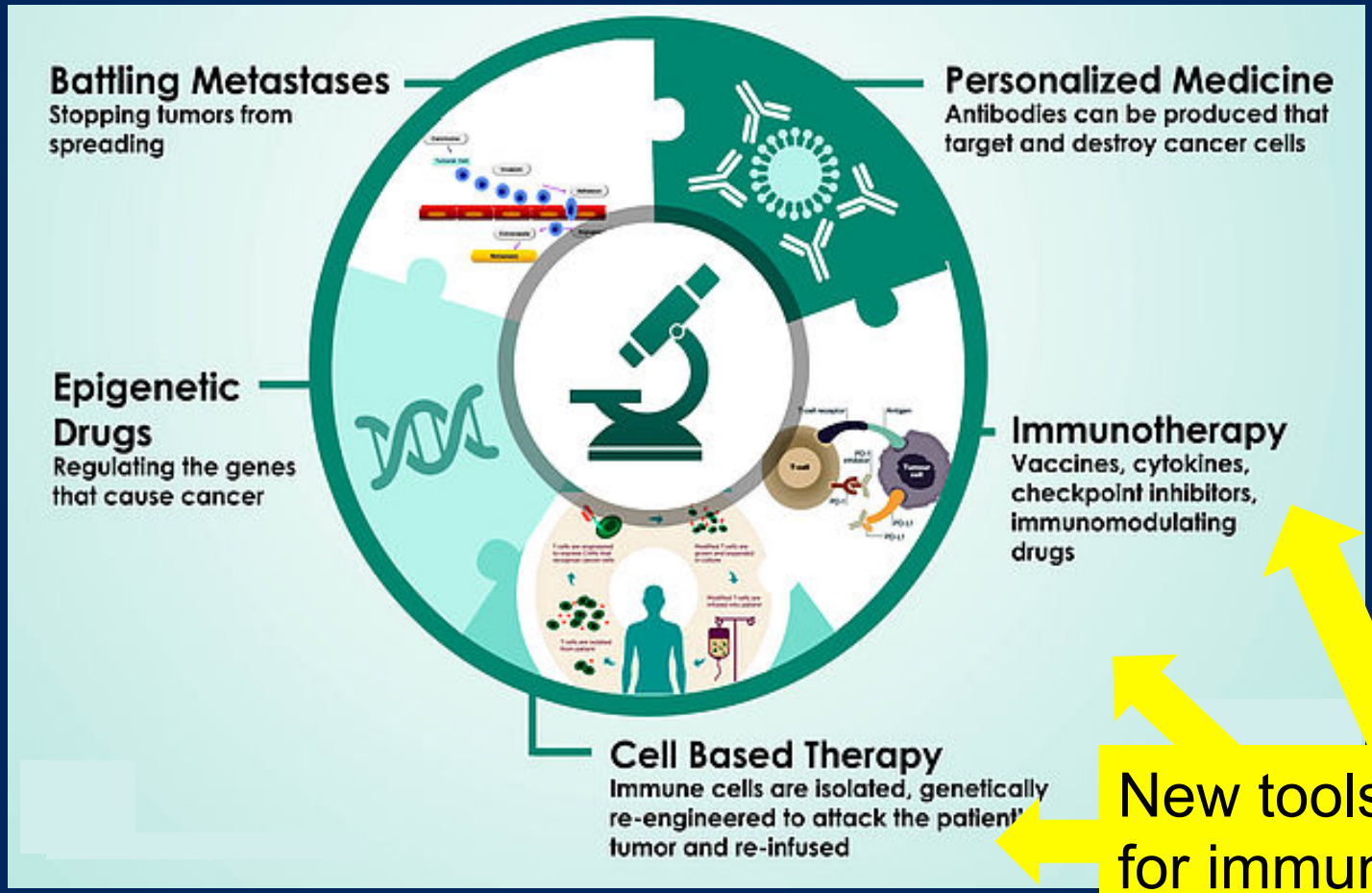
STAFF AND WIRE REPORTS | December 6, 2015 | Updated: December 7, 2015 3:44pm

Photo: KEVIN D LILES, STR

Former President Jimmy Carter talked about his cancer diagnosis in August.

ATLANTA - Former President Jimmy Carter, who has been undergoing treatment for cancer that was removed from his liver but had spread to his brain, said Sunday that he was free of the disease.

Future: Immunological monitoring



New tools needed for immunological monitoring