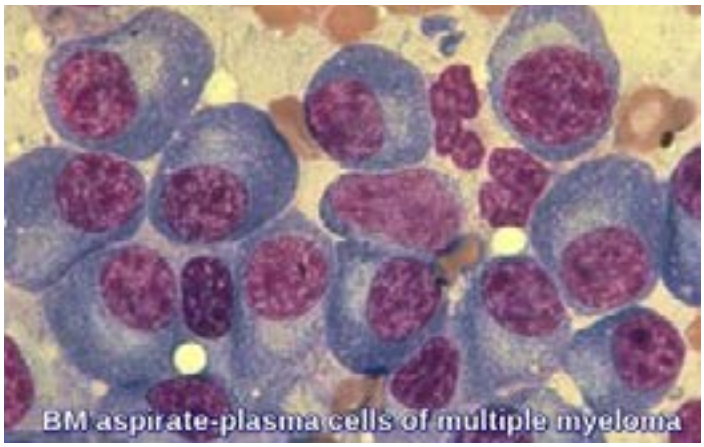
LIFESOUTH Community Blood Centers

L·s̄·I·R·L

Spring 2019 | LifeSouth s̄eries on Important Recent Literature

Is your patient using Monoclonal Antibody Therapy?

Using immunotherapy to treat hematologic malignancies and solid tumors is becoming more commonplace. This bulletin reviews the effects of monoclonal antibody (mAb) drugs on red blood cells and pretransfusion testing, as well as methods used to diminish them. There are more than 400 molecules already described currently being used as targets for cell immunophenotyping and to develop more precise immunotherapies. At this time, the two monoclonals we have encountered the most are anti-CD38 and anti-CD47.



askhematologist.com/multiple-myeloma/

In 2015, Darzalex® (Daratumumab or "Dara") became the first human anti-CD38 mAb approved by the FDA for the treatment of relapsed multiple myeloma. Currently anti-CD47 mAbs are undergoing clinical trials for multiple solid and hematologic malignancies, e.g., Hu5F9-G4, CC-90002, SFR231, and in 2018 the FDA granted SFR231 orphan drug designation for multiple myeloma.

CD38 is a glycoprotein found on the surface of many types of cells including B and T lymphocytes, natural killer (NK), plasma cells, platelets, and red blood cells, but is highly expressed in multiple myeloma plasma (MM) cells. CD38 functions as a receptor and adhesion molecule, as well as manufacturer and hydrolyzer of an intracellular calcium ion-activating messenger. The binding of anti-CD38 to CD38 inhibits the growth of MM cells and induces tumor cell death through a variety of immunological mechanisms.

Expressed on virtually all tissue and cell types, CD47 is a "marker of self" and functions as a "don't eat me" signal for phagocytic cells. As a consequence, transfused RBCs and platelets are protected from rapid clearance by splenic macrophages. In addition, CD47 expression decreases as RBCs age and is considered a marker of senescence. During treatment, anti-CD47 binds with CD47 and blocks this signal, permitting cell destruction of malignant cells by phagocytosis.

Interference in blood bank testing when samples contain anti-CD38:

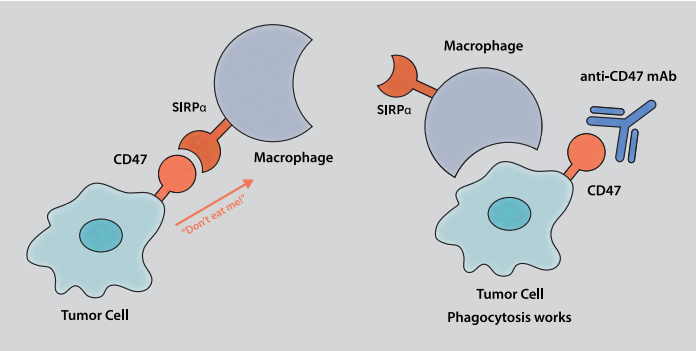
- Results from increased CD38 expression on RBC membranes of cancer patients and weak expression on normal RBCs.
- Immediate spin reactions are unaffected, but IAT tests by gel, tube, and solid phase are generally weakly positive (e.g., antibody screens, panels, and crossmatches). Interference can persist for six months following treatment.
- Autocontrol and DAT may be positive or negative, and results often resemble an antibody to a high incidence antigen or warm autoantibody.
- Adsorptions are not effective.
- It is important to perform pretransfusion testing, including an extended phenotype (either serological or predictive genotype), before initiating treatment.

Mitigation of anti-CD38 interference:

- Perform antibody screen using RBCs pretreated with dithiothreitol (DTT).
- DTT is a reducing agent that disrupts disulfide bonds formed between cysteine residues. The CD38 molecule (also on RBCs) has 5 disulfide bonds, so when a patient's plasma is tested with reagent red cells treated with DTT, reactivity from anti-CD38 is abolished.
- Anti-CD38 sometimes does not react with cord blood cells which have very little CD38.
- Recombinant soluble human CD38 or anti-daratumumab idiotype antibody can be utilized to eliminate interference, but is not widely available at this time.
- Kell, Knops, Dombrock, Lutheran, Yt (formerly Cartwright), and JMH blood group system antigens, as well as to the LW^a antigen, are destroyed by DTT; and thus cannot be excluded during antibody identification.

For patients with a negative antibody screen using DTT-treated RBCs, an electronic or immediate-spin crossmatch with ABO/RhD compatible units may be performed. Units negative for the K (KEL1) antigen should be issued if the patient is negative for this antigen, or the antigen typing is unknown.

For patients with known alloantibodies, antigen negative RBCs are provided. Antiglobulin crossmatches will be incompatible and local policies regarding ordering physician signature must be followed before transfusing blood products.



acrobiosystems.com/A1037-Leukocyte-Surface-Antigen-CD47

Interference in blood bank testing when samples contain anti-CD47:

- False positive reactions can be seen in all phases of testing (immediate spin, 37°C, and IAT) and with all forms of IAT testing (i.e., tube, gel, solid phase).
- ABO discrepancies occur resulting in false positives in the reverse typing (all types except for O) and false positives in the forward typing due to spontaneous agglutination of patient RBCs.
- DATs may be falsely negative due to a "blocking effect" caused by high levels of antibody present, but eluates are strongly positive.
- False negative phenotyping test results can occur due to RBCs heavily coated by anti-CD47.
- It is highly recommended to perform pretransfusion testing, including extended phenotype (either serological or predictive genotype) before initiating treatment.

Mitigation of anti-CD47 interference:

- Utilize an anti-IgG reagent that does not bind to IgG4, such as Anti-IgG (Murine Monoclonal)(Green or Uncolored) Gamma-clone® (Hu5F9-G4 and CC-90002 are monoclonal IgG4 anti-CD47).
- For other testing, the antibody must be removed from plasma via allogenic adsorption or adsorption using pooled platelets or papain treated RBCs. This generally requires four adsorptions.

Note: Similar to interfering in RBC antibody detection, plasma containing anti-CD38 or anti-CD47 may also affect detection of antibodies to HLA Class I and platelet antigens, as well as interfere with platelet crossmatch testing.* No CD47 in Rh null cells.

What the IRL needs:

Before submitting a workup to the Immunohematology Reference Laboratory (IRL), obtain an accurate and complete patient diagnosis and history, this can help avoid unnecessary delays in obtaining results as well as charges for unnecessary testing.

- Always include medication lists when available. This is especially true when the patient has a diagnosis of MM or any other type of leukemia/lymphoma or solid tumor.
- To the extent possible, be familiar with new drugs under development.
- Anything ending in "mab" is a monoclonal antibody.
- Anything starting with "anti" might be an antibody.

Anything named with an odd string of letters and numbers might be an investigational drug. Beware that conditions such as "anemia," "shortness of breath" and "thrombocytopenia" are not diagnoses. To obtain the diagnosis, consult with the patient's physician or healthcare team.

NOTE: Some patients visit multiple hospitals and relevant history may be obtained from another facility, if known.
****** Complete patient demographics and transfusion and medication history on IRL orders will improve efficiency and the costs of testing.***

For more information, please refer to the following **I**mportant **R**ecent **L**iterature in *Transfusion* (Volume 59, Issue 2, February 2019) and other peer reviewed journals.

Monoclonal anti-CD47 interference in red cell and platelet testing PMID: 30516833

Immunotherapy: the good, the bad, the ugly, and the really ugly PMID: 30727039

Monoclonal antibodies targeting CD38 in hematological malignancies and beyond. Niels et al, Immunol Rev. March 2016. PMID: 26864107

CD38 antibodies in multiple myeloma: back to the future. Van de Donk et al, Blood, February 11, 2016. 127 (6) https://doi.org/10.1182/blood-2017-06-740944. **PMID: 29118010**

Clinical Trials Using Anti-CD47 Monoclonal Antibody Hu5F9-G4. National Cancer Institute. https://www.cancer.gov/about-cancer/treatment/clinical-trials/intervention/anti-cd47-monoclonal-antibody-hu5f9-g4

Jonathan Hoggatt. ***Anti-CD47 Therapy Is More Than a Dinner Bell.*** The Hematologist: ASH News and Reports. November-December 2015, Volume 12, Issue 6

Engel P et al. CD Nomenclature 2015: Human Leukocyte Differentiation Antigen Workshops as a Driving Force in Immunology. J Immunol. 2015 Nov 15;195(10):4555-63. doi: 10.4049/jimmunol.1502033 http://www.jimmunol.org/content/195/10/4555 **PMID: 26546687**

CD47 blockade triggers T cell-mediated destruction of immunogenic tumors. Liu X, Pu Y, Cron K, Deng L, Kline J, Frazier WA, Xu H, Peng H, Fu YX, Xu MM. Nat Med. 2015 Oct;21(10):1209-15. doi: 10.1038/nm.3931. Epub 2015 Aug 31. **PMID: 26322579**