# Granulocyte Transfusions: A Clinician's Perspective

## Is there a role for this therapy?

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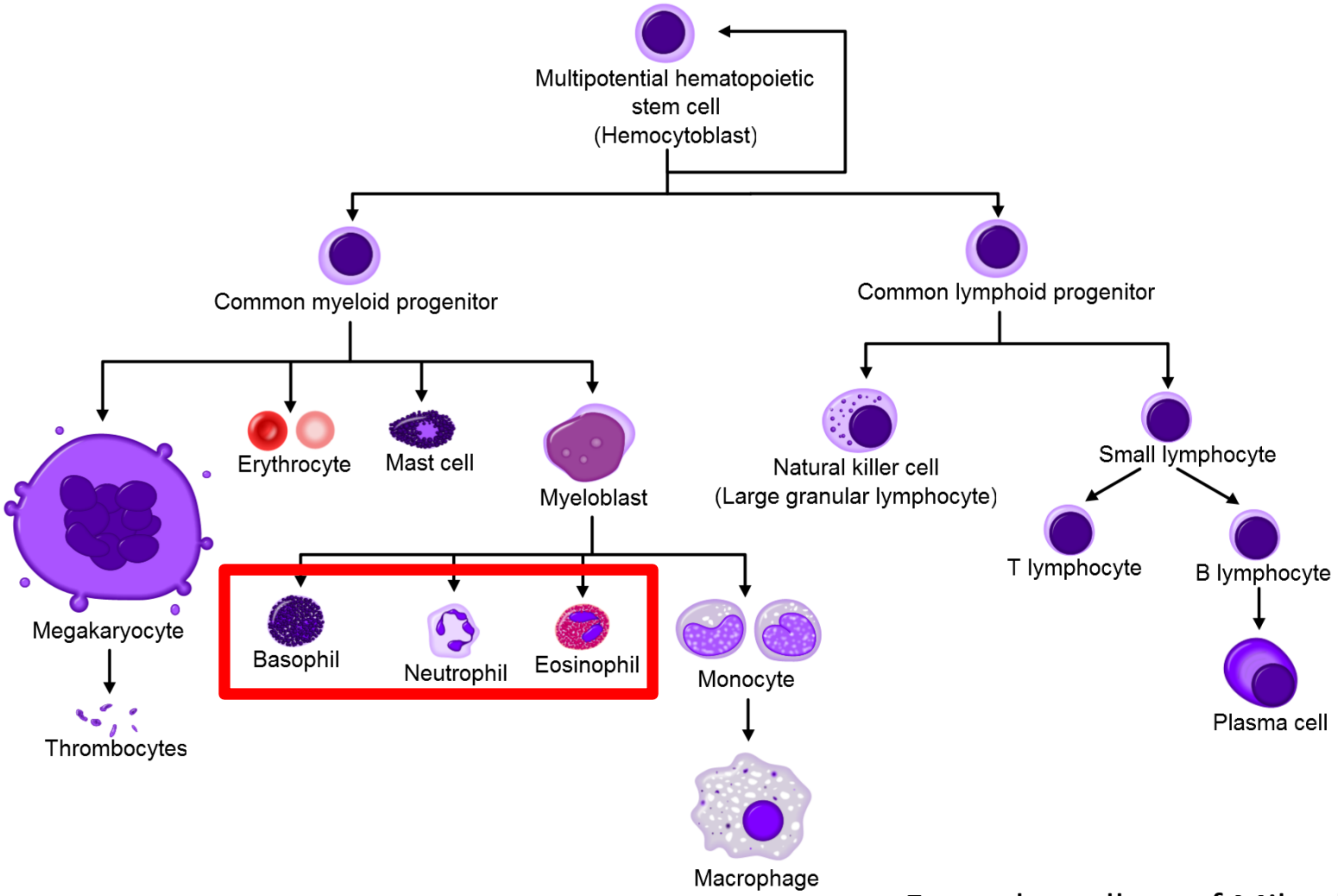
# Objectives

- Understand the rationale for granulocyte transfusion (GTX)
- Understand the controversy around efficacy and role of GTX
- Understand the ethical implications of the therapy

# Outline

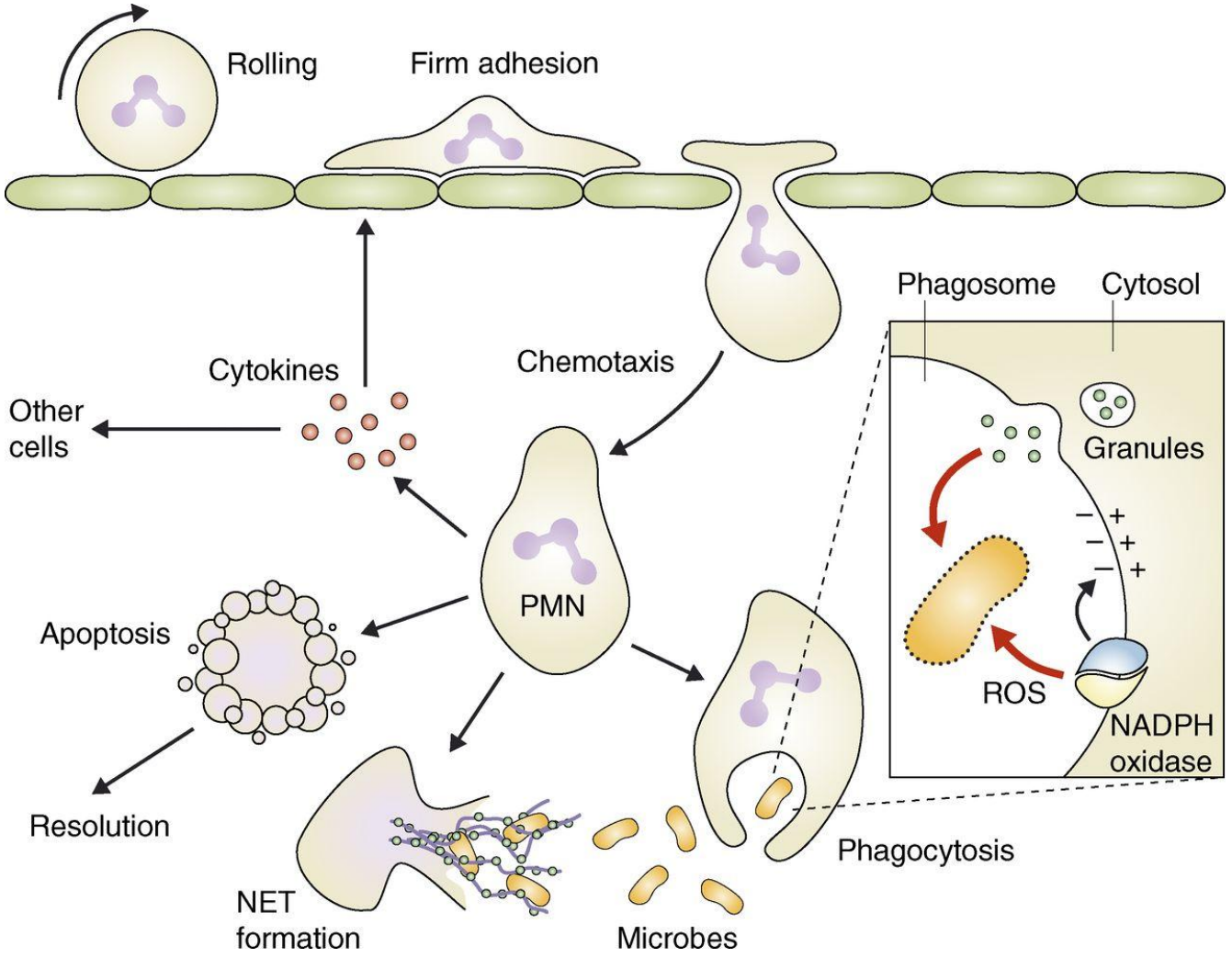
- Background and Rationale
  - Prophylactic vs Treatment
- Brief review/summary of data
- Cases
- Discussion

# Background



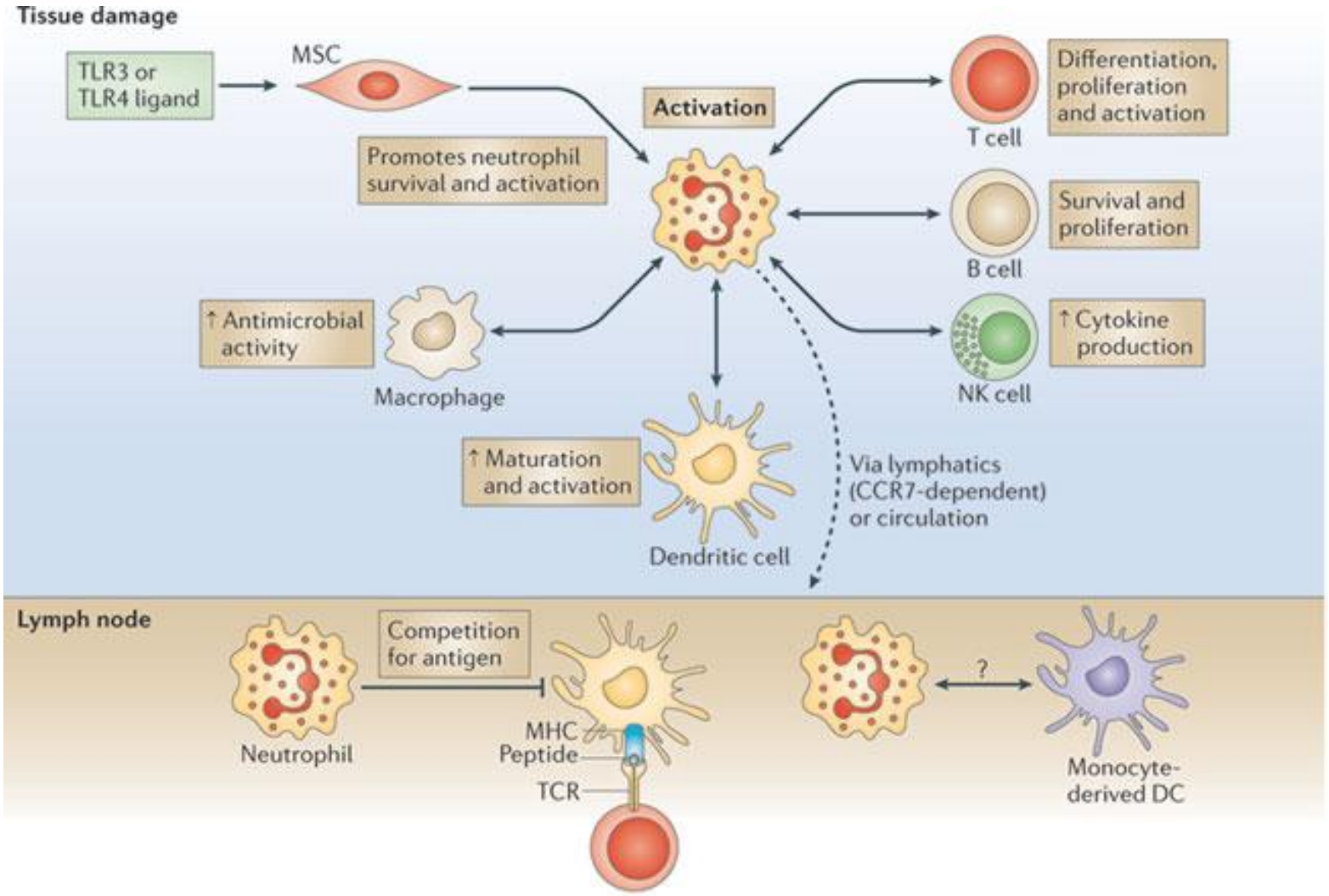

From the gallery of Mikael Haggstrom

# Neutrophil Chemotaxis

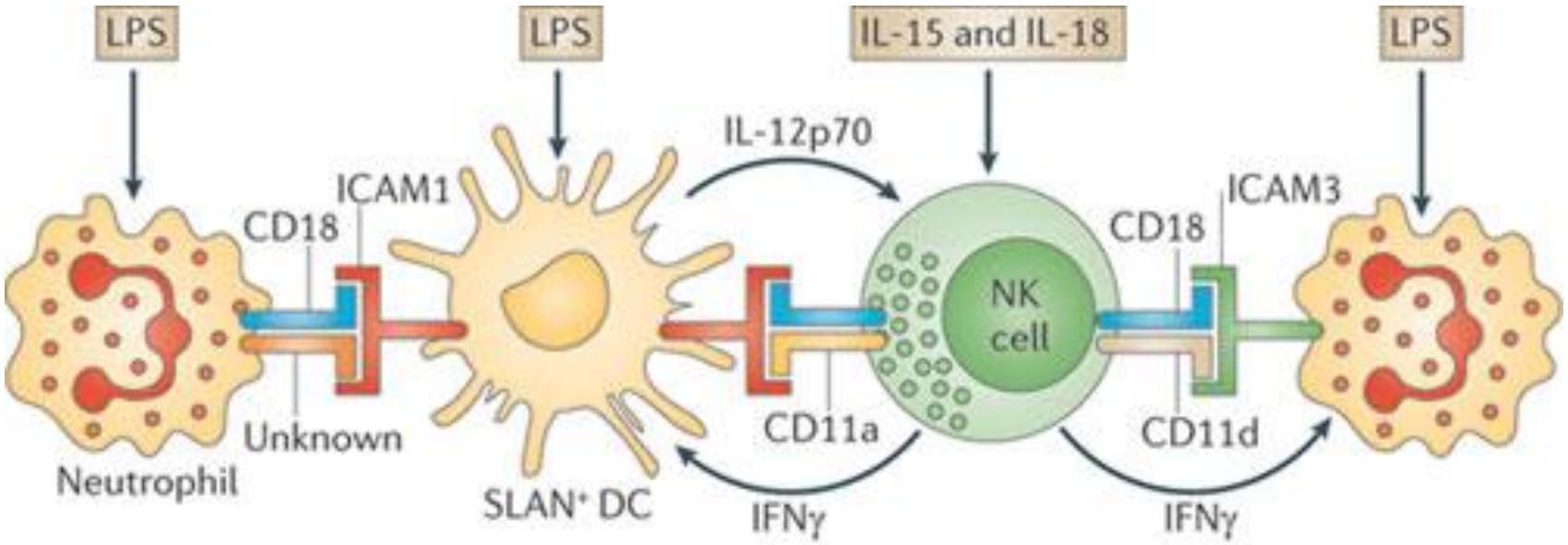



**Attila Mócsai J Exp Med 2013;210:1283-1299**

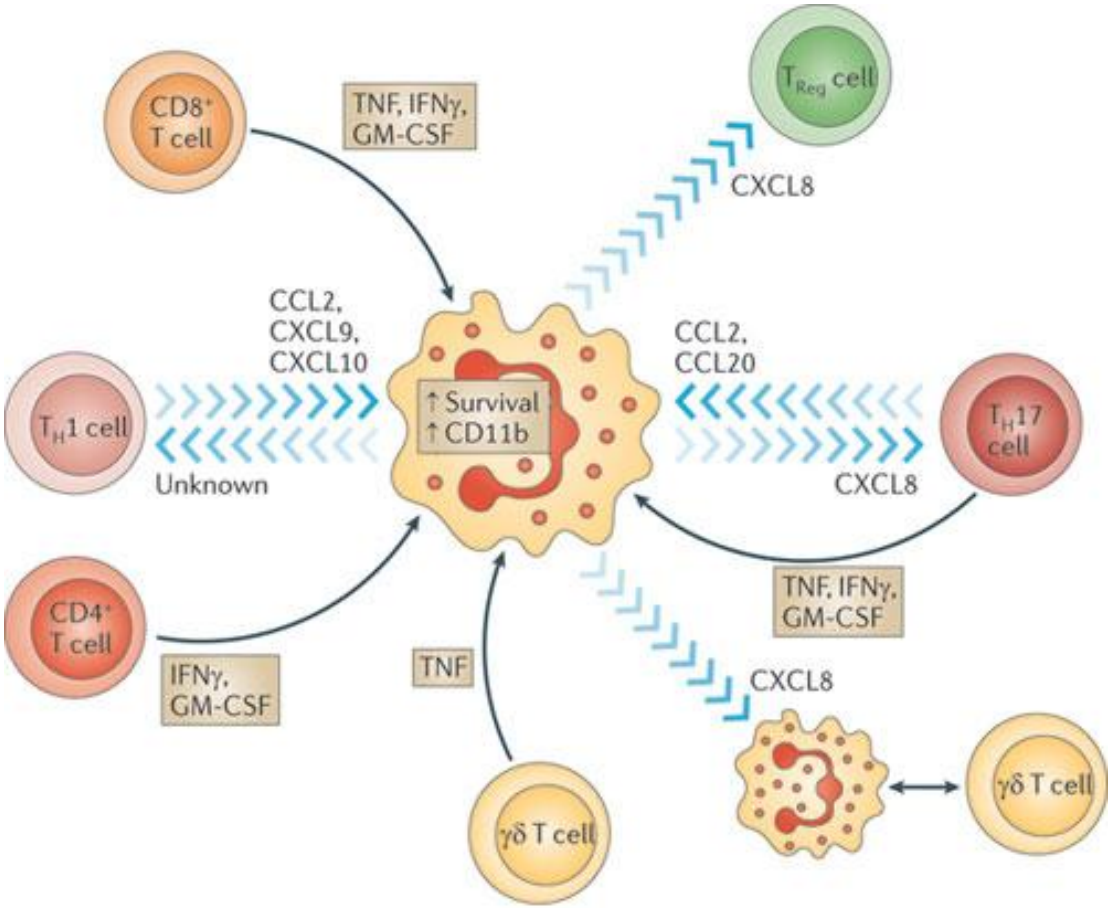
# Neutrophil Crosstalk



# Neutrophil Crosstalk
# Innate Immunity

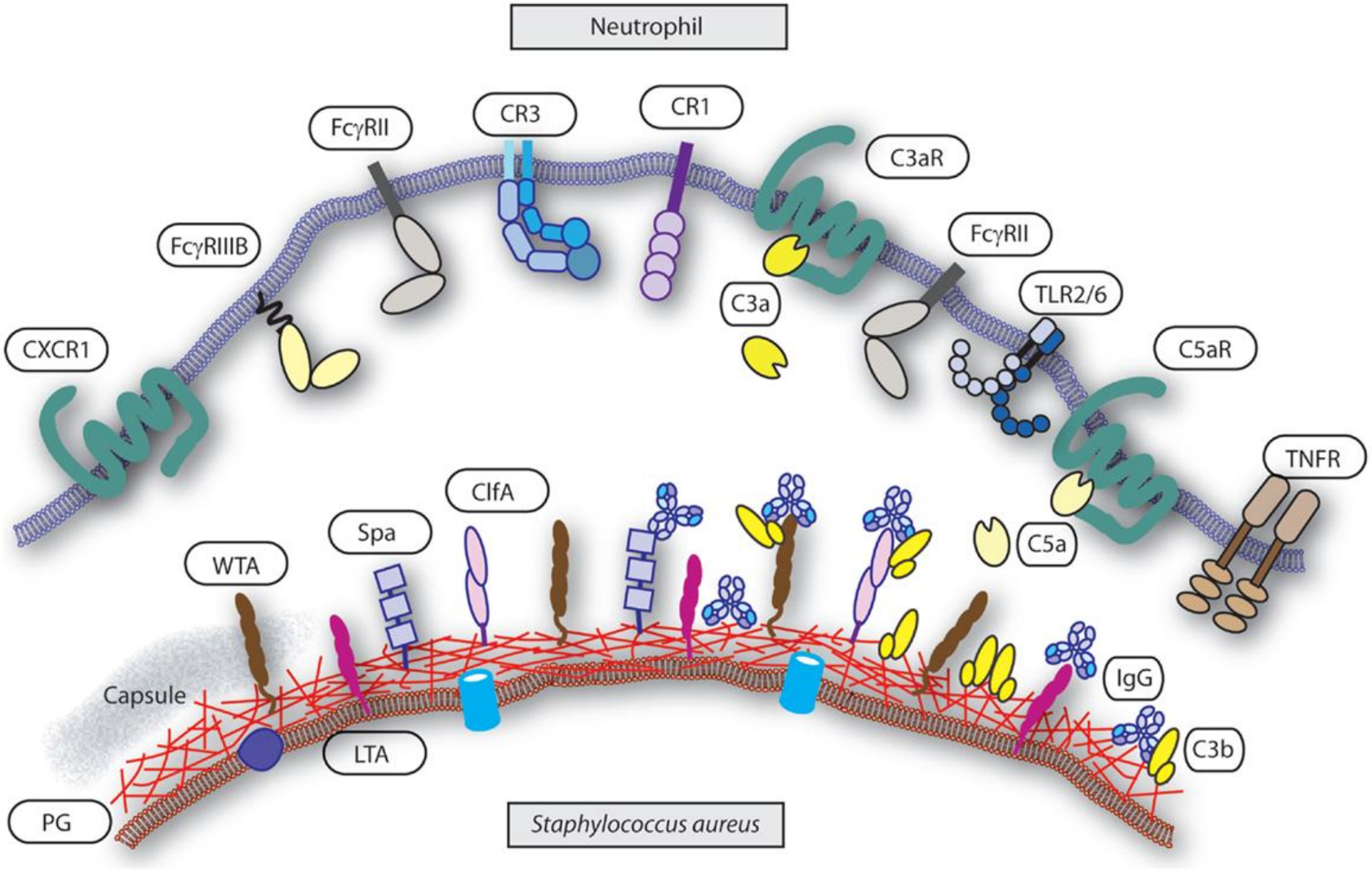


# Neutrophil Crosstalk Lymphocytes



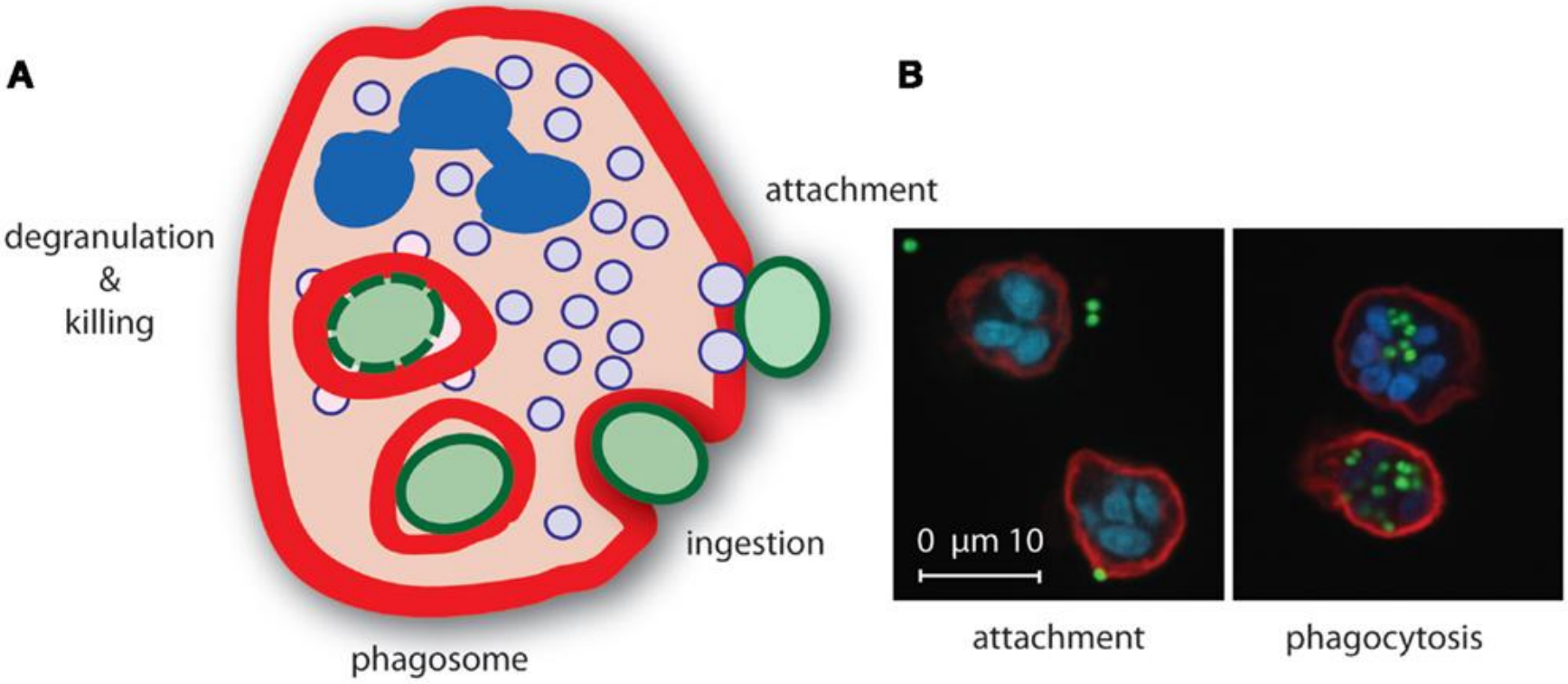

Nature Reviews | Immunology

# Neutrophil Interaction with Pathogen




Van Kessel et al. Neutrophill-mediated phagocytosis of Staphylococcus aureus. Front Immunol. 26 Sept 2014

# Phagocytosis




Van Kessel et al. Neutrophill-mediated phagocytosis of Staphylococcus aureus. Front Immunol. 26 Sept 2014

# Examples of Neutrophil Disorders Congenital/Hereditary

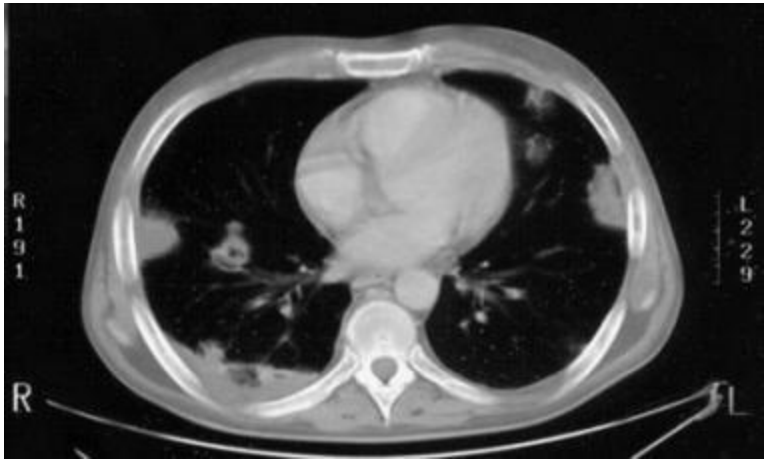
- Chediak-Higashi Syndrome (chemotaxis and killing)
- Chronic Granulomatous Disease (killing defect)
- Kostmann Syndrome (agenesis)
- LAD-I and II (chemotaxis defect)

# Neutrophil Disorders Acquired

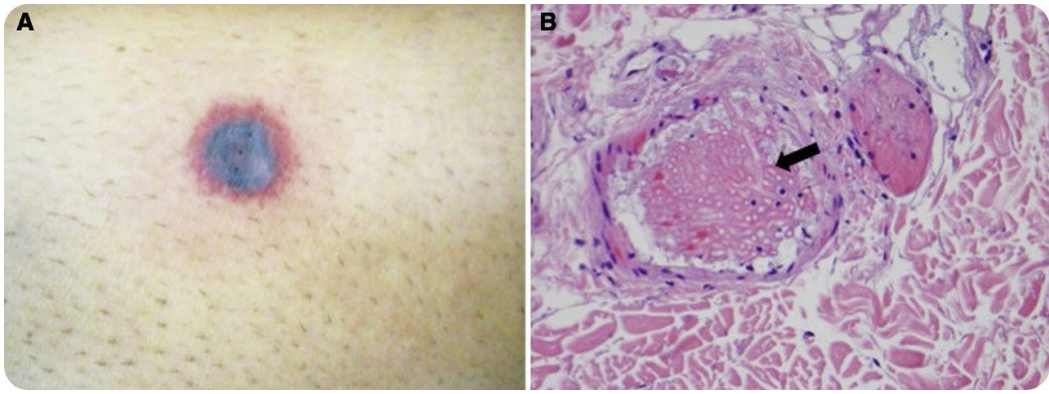
- Neutropenia due to:
  - Medication induced
    - May be autoimmune or direct drug effect
  - Autoimmune
  - Aplastic Anemia (immune mediated)
  - Malignancy induced
  - Chemotherapy induced

# Consequences

- Increased susceptibility:
  - Bacteria
  - Fungi

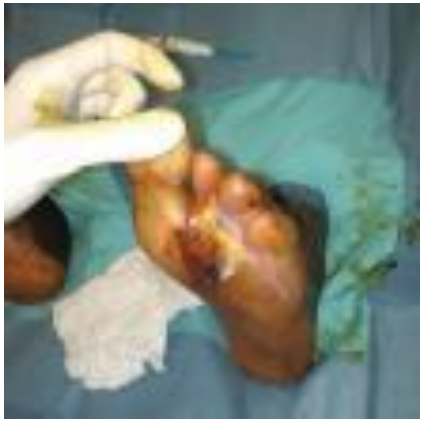



**Fungal Pneumonia Overview of Fungal Pneumonia (Medscape Aug 2014)**
Author: Romeo A Mandanas, MD, FACP; Chief Editor: Ryland P Byrd, Jr, MD




**Amitkumar Mehta, and Naresh Bellam Blood 2014;123:3379**

blood



McCurdy, B Podiatry Today. July 2006; Vol 19 (7)

# Standard Therapies

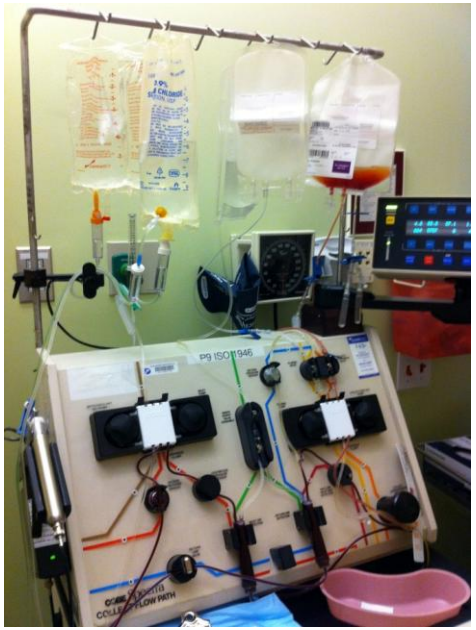
- Significant advances in anti-microbial therapy
  - Broad spectrum antibacterial prophylaxis
  - Broad spectrum antifungal prophylaxis
  - Better understanding of combination therapies and resistance
- Understanding who needs closer monitoring
  - Association of infection risk with therapy
    - AML vs ALL therapy

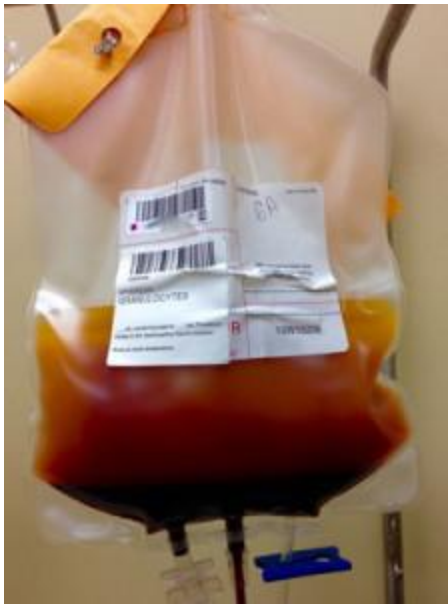
# Rationale for GTX

- Neutropenia leads to these infections
- Antimicrobial resistance is always threatening
- Resistance is already present
- Mortality with advanced infections is high
- Why not replace the neutrophils/granulocytes?
  - We have the technology……we can replace them.
  - Should we prophylax or just treat?

# Acquisition of Granulocytes

- ABO compatible donor
- HLA matched if recipient has HLA antibodies
- Donor questionnaire
- Steroid and GCSF stimulation
  - GCSF 600ug/Dex 8mg
  - 12-16 hrs pre-harvest
- Leukapheresis
- CMV status?
- No leukoreduction
- Irradiate
- HES (hydroxyethylstarch improves separation)
- Target 1-5x10e10 cells/collection





# Dosing and Early studies

- Early studies suggested a dose response curve
  - Lowenthal et al. 1975 The Lancet
    - 4x granulocyte dose associated with response vs non-response
  - Alavi et al. NEJM 1977
    - Randomized to abx vs abx + GTX
      - 21 d survival 20% vs 75% in infected patients
      - 21 d survival 79% vs 88% if no confirmed infection
      - All got approx 5x10e10 cells per infusion
- Toxicities
  - Primarily pulmonary
  - GVHD if not irradiated

# 1980’s and 90’s

- Significant decrease in GTX
  - Questionable efficacy
  - Difficult to collect
  - Costly
  - Improvement in antimicrobial prophylaxis and therapy

# Other Issues With GTX

- Donor Risks
  - GcSF
    - Bone pain
    - Headache
    - Fatigue
    - Myalgia
    - ? Postcapsular cataract
- Recipient Risks
  - Fever, chills, pulmonary edema
  - Hypotension, nausea/vomiting, TRALI
- Cost
  - Estimated $2000-4800/GTX
    - Kadri et al. Role of granulocyte transfusions in invasive fusariosis: systematic review and single-center experience. Transfusion 2015;55;2076-2085

# Renewed Interest

- Improved yield
- More resistant infections

# Prophylaxis- Evidence?

- Granulocyte transfusions for preventing infections in people with neutropenia…
  - Estcourt et al. Cochrane Database Review 2015
  - Eval'd 9 manuscripts of RCT's/quasi RCT's for meta-analysis
    - Patients received GTX or not
  - Results:
    - No difference in all cause mortality or mortality due to infection
    - Decreased bacteremia/fungemia and infection with intermediate dosing
    - Serious Adverse Events: Pulmonary; graft vs host disease x1 in unirradiated product.
  - Conclusion: There is low-quality evidence that prophylactic GTX decrease the risk of developing a bacterial or fungal infection

# GTX for Treatment of Neutropenic Infections

- Stanworth et al. Cochrane Reviews 2005. July 20; (3)
- Evaluated 8 parallel RCT's
- Inconclusive evidence to support or refute use of GTX in neutropenia due to chemotherapy
- Future studies should dose >1x10e10/transfusion

# RING Study

(Resolving Infection in Neutropenia with Granulocytes)
Price et al. Blood, 29 October 2015 Vol 126, No 18

- Designed to eval effect of high-dose GTX
- Anti-microbials vs Anti-microbials + GTX

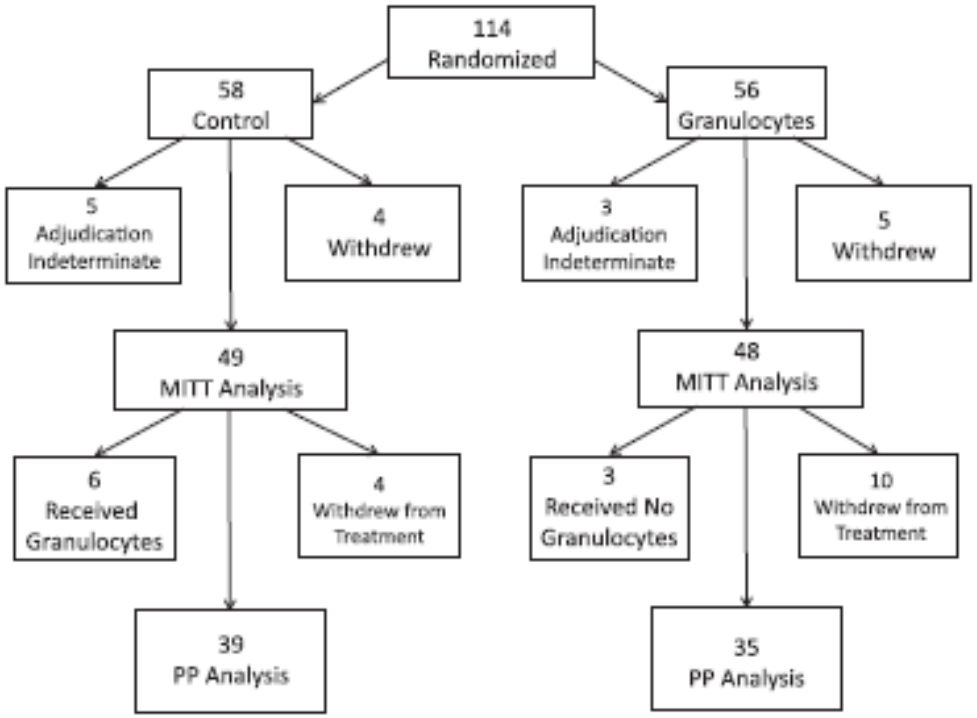
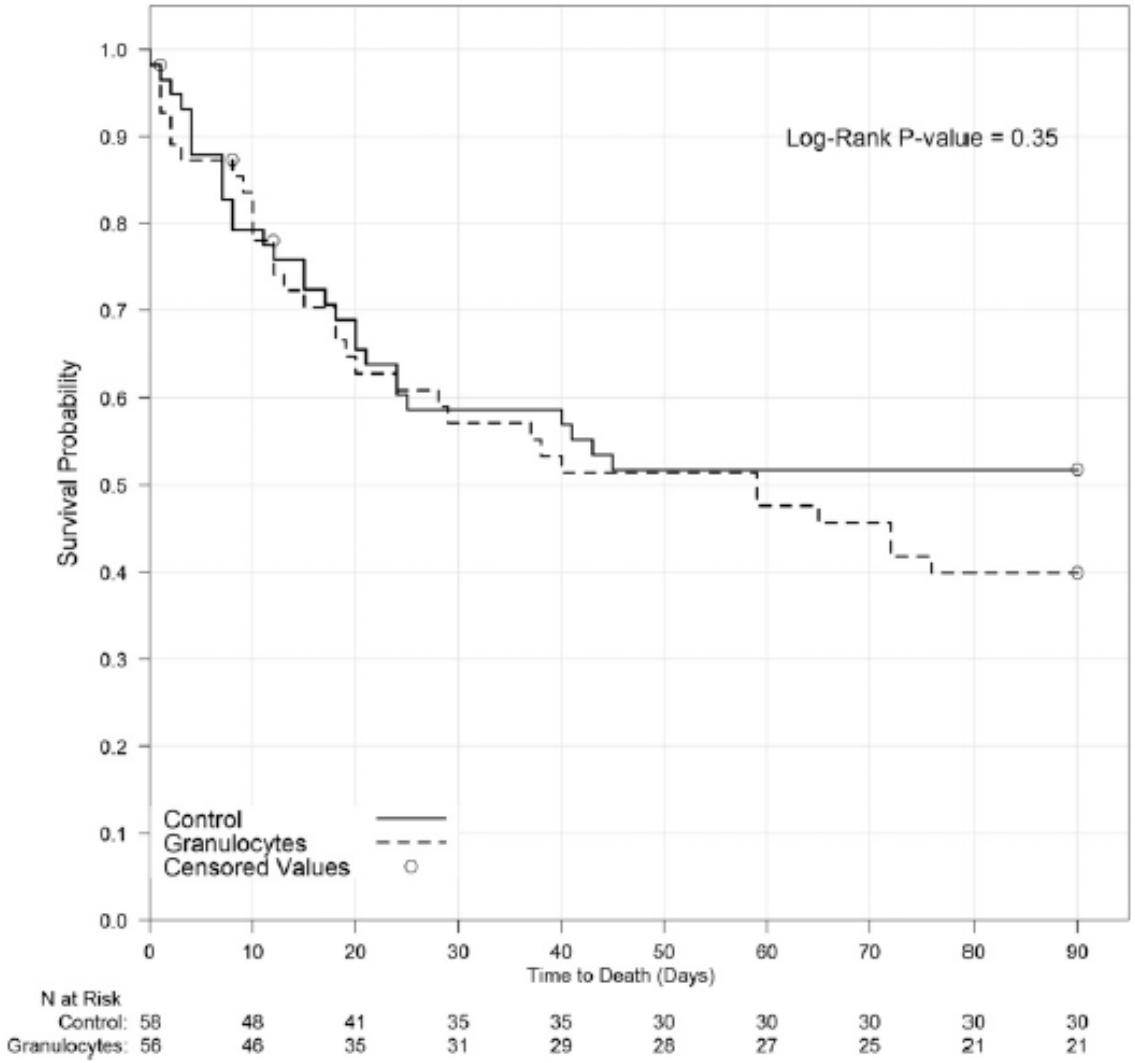


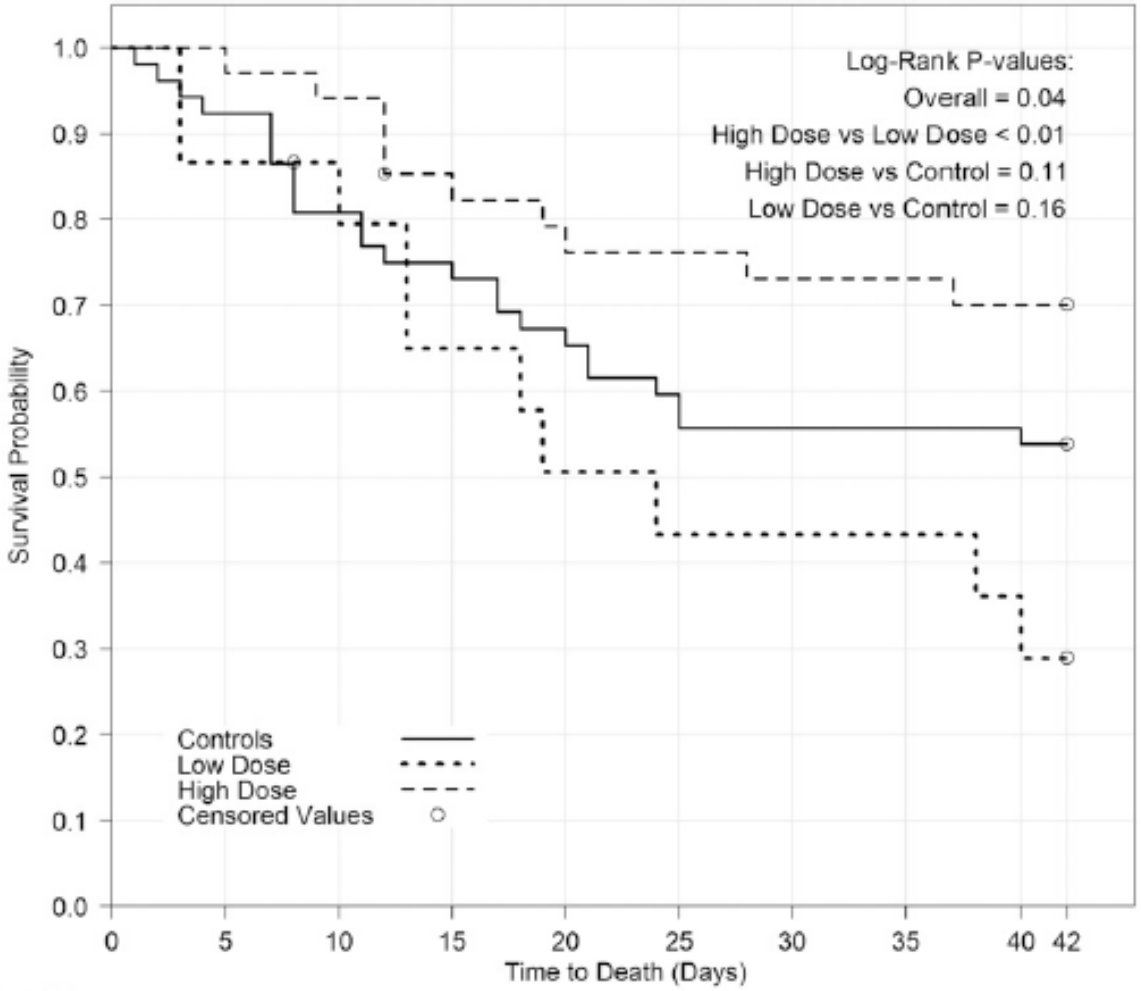

**Figure 1. Flow diagram of the study.** A total of 114 patients were randomized, 56 to the granulocytes group and 58 to the control group. Nine subjects withdrew from the study, and an additional 14 subjects withdrew from treatment.

# Primary Outcome

**Figure 5. Survival to 90 days by treatment arm.** Analyzed using Kaplan-Meier methodology. Three subjects were censored prior to day 90 due to missing information.



# Sub-group Analysis




| N at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| High Dose: | 34 | 34 | 32 | 28 | 26 | 25 | 24 | 24 | 23 | 23 |
| Low Dose: | 15 | 13 | 12 | 9 | 7 | 6 | 6 | 6 | 5 | 4 |
| Control: | 52 | 48 | 42 | 39 | 35 | 31 | 29 | 29 | 29 | 28 |

**Figure 6. Survival to 42 days by dose group.** Analyzed using Kaplan-Meier methodology. Two subjects were censored prior to day 42 due to missing information.

# RING Study Conclusions

- Limitations:
  - Low accrual rate (Less than half of subjects needed to provide 80% power to detect 20% difference)
  - Dose of granulocytes
    - Targeted 4x10e10/dose
    - <75% got targeted dose
- If decision is made to provide GTX, ensure high doses of granulocytes

# So What Should Clinicians Do?

- Prophylaxis?
- Treatment?
  - Certain populations?
- Ethical?
  - Resource intensive
  - Risk to donors

# Cases

# Possible Roles?

- Many attempts to understand the role of GTX
- No definitive answer
- Studies suggest there may be a niche for use of GTX in treatment
  - Surrogate markers for response?
    - CRP (c-reactive protein) decrease after GTX
      - Grigull et al. Support Care Cancer (2006) 14:910-916
  - Bridge to definitive therapy?

# Personal Practice

- In the presence of neutropenia:
  - Definitive treatment plan in place or anticipated
  - Documented fungal infection that is life threatening and refractory to therapy
  - Wound/abscess that is healing poorly despite optimal medical therapy
- Very concerned about risks to donors given controversy
- Very open to constructive criticism and ideas for studies.

# Thank You

- To the organizers
- To the investigators
- Especially to the donors

# Contact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