The Impact of Gut Microbiome on Transplant or CAR T-cell Therapy

Celebrating a Second Chance at Life Survivorship Symposium

May 3-9, 2025

Melody Smith, MD, MS
Stanford Medicine

The Impact of Intestinal Microbiome on Transplant or CAR T-cell Therapy

Celebrating a Second Chance at Life Symposium
May 5, 2025

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Disclosures

- Patents regarding the intestinal microbiome in relation to CAR T cell therapy
- Advisory Board: A28 Therapeutics
- Consultancy: CVS Caremark

Objectives

- The role of the intestinal microbiome in outcomes following allogeneic hematopoietic cell transplantation (allo-HCT) or chimeric antigen receptor (CAR) T cell therapy
- The impact of allo-HCT and CAR T cell therapy on the intestinal microbiome
- Interventions, including diet and lifestyle changes, that promote a healthy microbiome

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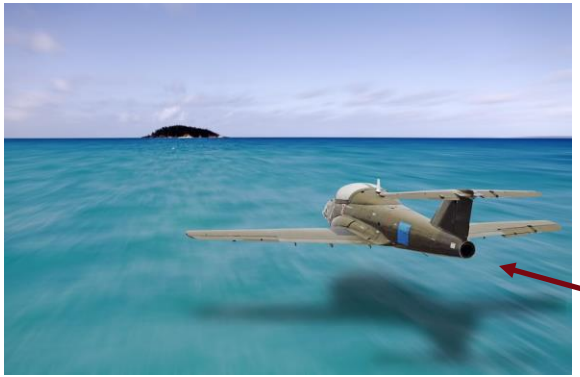
Cancer Immunotherapy

Radar Detection of the Immune System



Cancer Immunotherapy

Cancer

Cancer immunotherapy is a class of cancer treatments that enhance the immune system's ability to fight cancer

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Cancer Immunotherapy

Allogeneic hematopoietic cell transplant (allo-HCT)

Immune Checkpoint Blockade (anti-PD-1, anti-CTLA-4)

Adoptive cellular therapy (CAR and TCR)

CAR: chimeric antigen receptor
TCR: T cell receptor

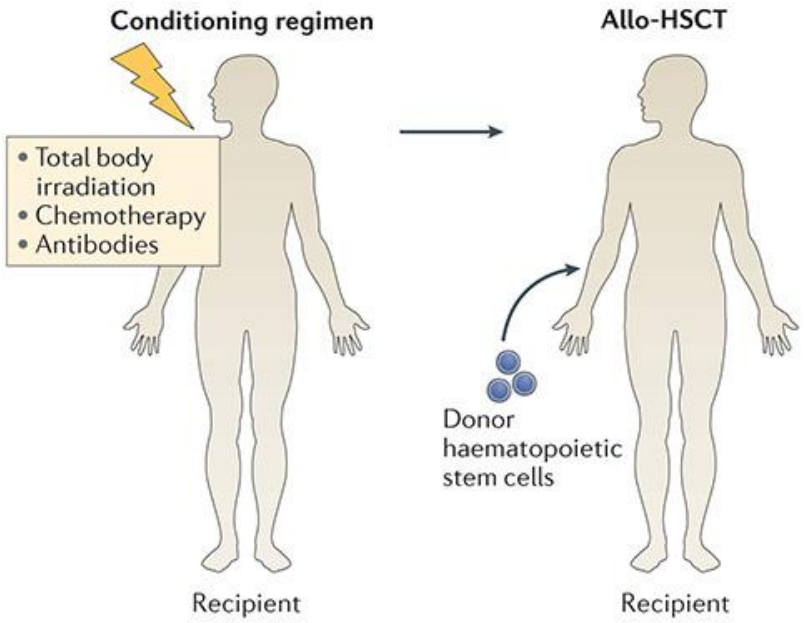
Cancer Immunotherapy

Allogeneic hematopoietic cell transplant (allo-HCT)

Immune Checkpoint Blockade (anti-PD-1, anti-CTLA-4)

Adoptive cellular therapy (CAR and TCR)

Allo-HCT for Blood Cancers



Shono Y and van den Brink RM. Nat Rev Cancer 2018

Conventional allo-HCT

- Recipient receives all the cells from the transplant donor
- No removal of specific cells, such as T cells
- Rate of acute graft-versus-host disease (GVHD) ranges from 40-60%

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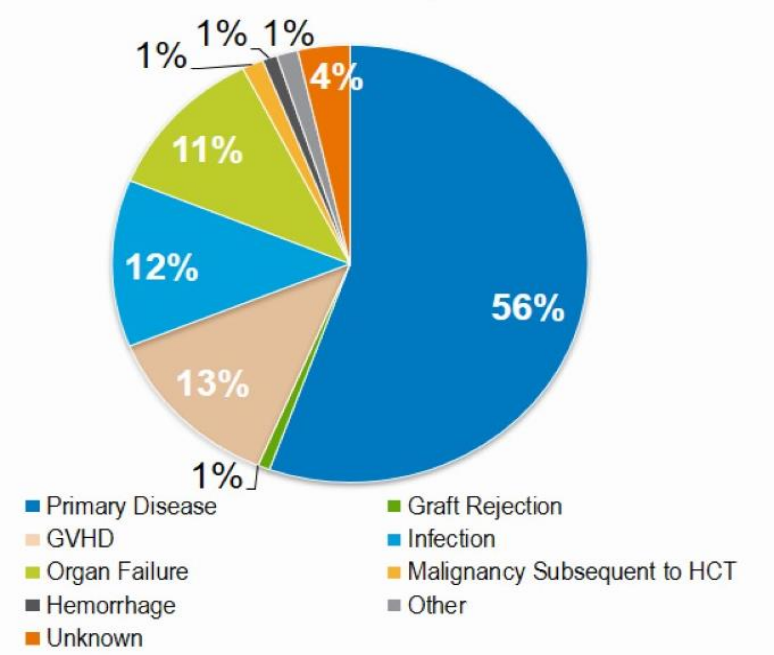
Relapse and GVHD following Allo-HCT

Mortality 1-year post-allo-HCT



CIBMTR summary 2020

- Relapse and GVHD are the leading causes of death following allo-HCT
- Much of allo-HCT research focuses on strategies to:
  1. enhance graft-versus-leukemia (GVL) activity and
  2. mitigate GVHD

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Cancer Immunotherapy

Allogeneic hematopoietic cell transplant (allo-HCT)

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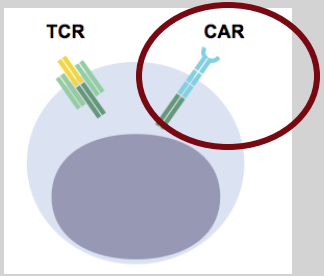
CAR: chimeric antigen receptor
TCR: T cell receptor

The Chimera in Greek Mythology

- In Greek mythology, the Chimera was a fire-breathing hybrid creature consisting of –
  - The head and body of a lion,
  - The head of a goat protruding from its back,
  - A tail that might end with a snake's head

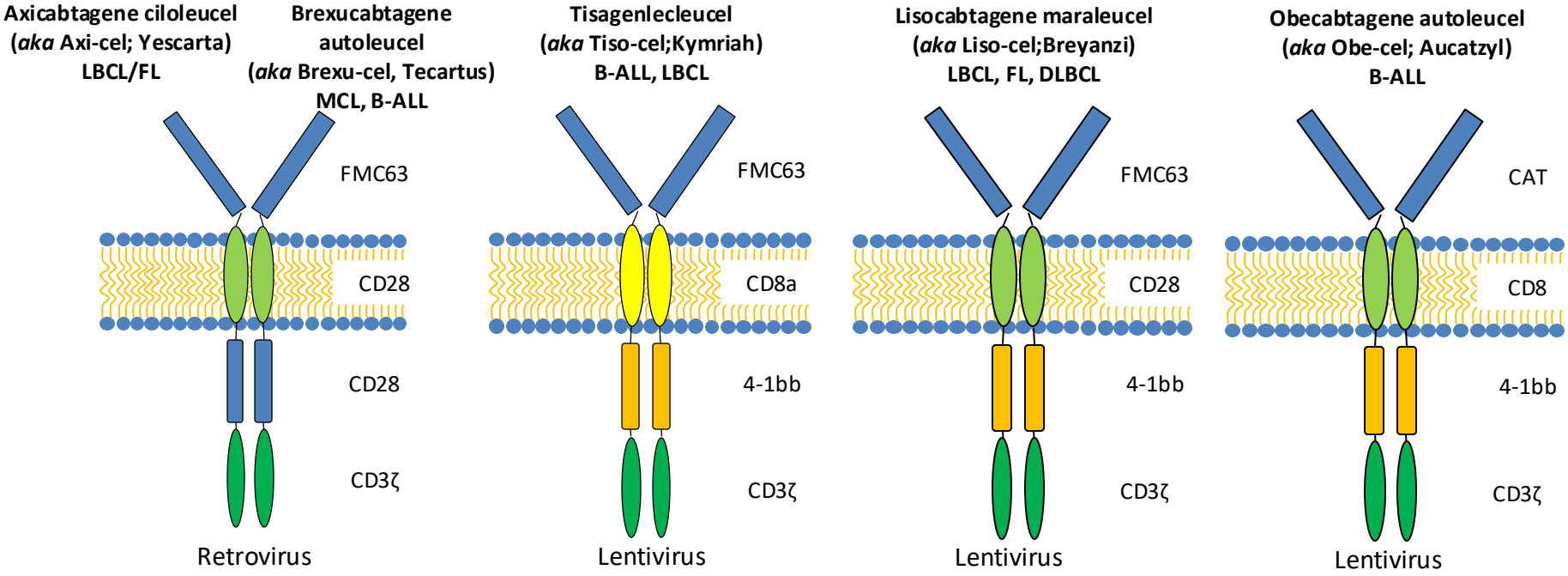
Chimeric Antigen Receptor (CAR)



- The CAR receptor is often introduced into the T cell using viral technology.
- The portion of the receptor outside the cells binds to the antigen, which is a marker on the tumor.

Credit: Musée du Louvre

Five CD19 CAR T-cell Constructs Approved by the FDA



Indications include NHL and B-ALL

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Adapted from van der Stegen, SJ et al. *Nat Rev Drug Discov* 2015

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Advancements in CAR T Cell Therapy for Hematologic Malignancies

- CAR T cells have revolutionized the treatment of patients with relapsed or refractory hematologic malignancies
- Seven CAR T cell products targeting CD19 or BCMA are FDA approved for B-cell malignancies and multiple myeloma, respectively

Credit: Emily Whitehead Foundation

HEALTH

Two patients declared 'cured' of leukemia, a decade after innovative treatment that has transformed blood cancer care

Karen Weintraub
USA TODAY

Published 12:31 p.m. ET Feb. 2, 2022 | **Updated 3:39 p.m. ET Feb. 3, 2022**

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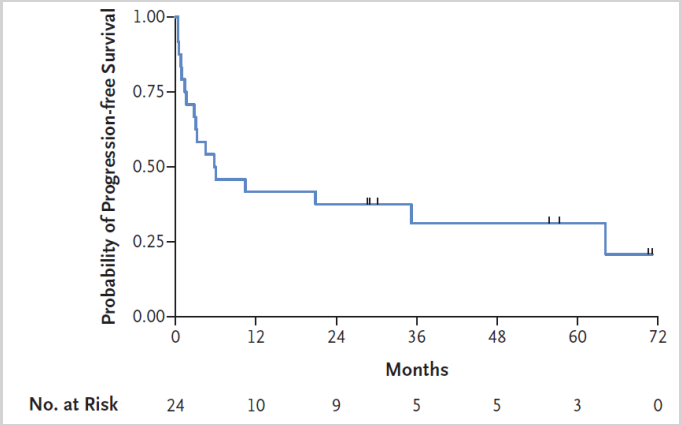
Limitations of CAR T cell Therapy

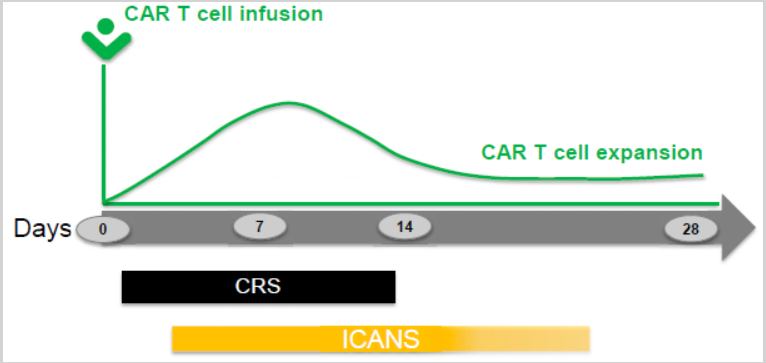
Disease relapse



Up to 60% of CAR T cell recipients experience disease relapse

Chong, E. et al. *NEJM* 2021

CRS and ICANS



Up to 80% of patients experience CAR-mediated toxicities – CRS or ICANS

Santomasso, B. et al. *Am Soc Clin Oncol Educ Book* 2019

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Advancements in Cellular Therapies for Hematologic Malignancies

- Given these limitations of cell therapies, we are investigating ways to improve patient outcomes.
- One approach we are focusing on is whether endogenous factors – factors within the host – alter patient response.
- One of these endogenous factors that we are interrogating is the impact of the intestinal microbiome.

What is the Intestinal Microbiome?

June 2012

The microorganisms that live in the human body, including –

- Bacteria
- Viruses
- Fungi

Interesting Facts

- 10^{14} microbes per person
- Makes up 3% of the human body mass
- 99% of microbes reside in the GI tract

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Cancer Immunotherapy

Allogeneic hematopoietic cell transplant (allo-HCT)

Immune Checkpoint Blockade (anti-PD-1, anti-CTLA-4)

Adoptive cellular therapy (CAR and TCR)

Allo-HCT: Taur Y, et al. *Blood* 2014; Jenq R, et al. *BBMT* 2015; Peled J, et al. *NEJM* 2020 **Immune Checkpoint Blockade:** Vétizou M, et al. *Science* 2015; Gopalakrishnan V, et al *Science* 2018; Matson V, et al. Science 2018; Routy B, et al. *Science* 2020

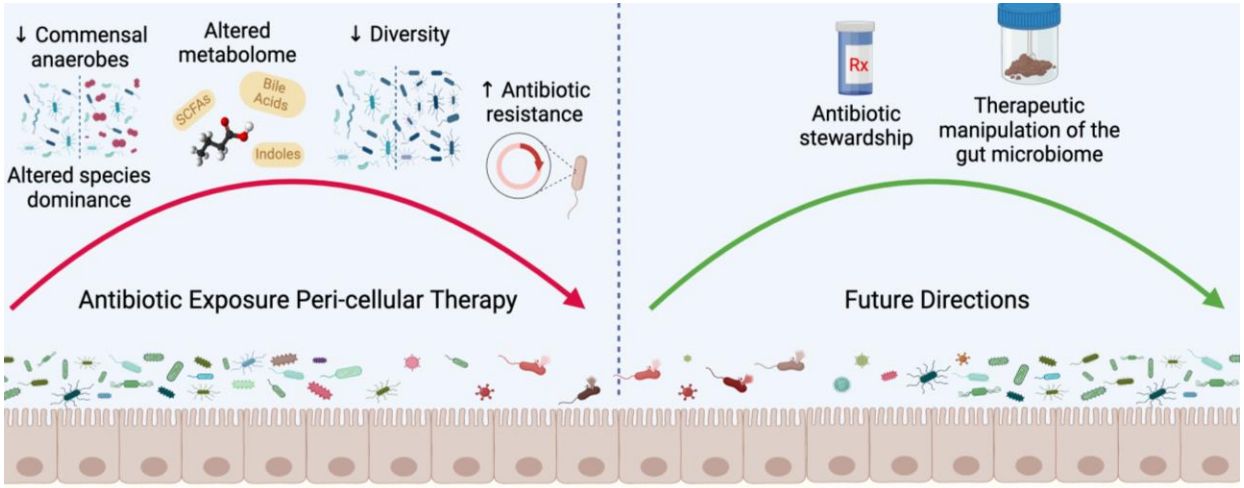
Summary I: Cancer Immunotherapy and the Intestinal Microbiome

- Cancer immunotherapies are a class of cancer treatment that enable the immune system to target cancer that may have otherwise gone undetected by the immune system.
- Allo-HCT and CAR T cell therapy are cancer immunotherapies that offer key therapeutic options for patients with blood cancers.
- The intestinal microbiome, which consists of the bacteria, viruses, and fungi in the host, has been implicated in the patient's response to these therapies.

Objectives

- The role of the intestinal microbiome in outcomes following allo-HCT or CAR T cell therapy
- The impact of allo-HCT and CAR T cell therapy on the intestinal microbiome
- Interventions, including diet and lifestyle changes, that promote a healthy microbiome

The Intestinal Microbiome: HCT and CAR T cells



Antibiotics Induce Dysbiosis and Impair Cellular Therapy Outcomes

Hematopoetic Cell Transplant

- Increased mortality due to acute gastrointestinal graft-versus-host disease (GVHD)
- Increased antibiotic resistance

CAR-T Cell Therapy

- Decreased progression free and overall survival
- Increased immune effector cell-associated neurotoxicity syndrome (ICANS; neurotoxicity)

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Darwin A, Xie J, and Smith M, *Blood Adv* 2025

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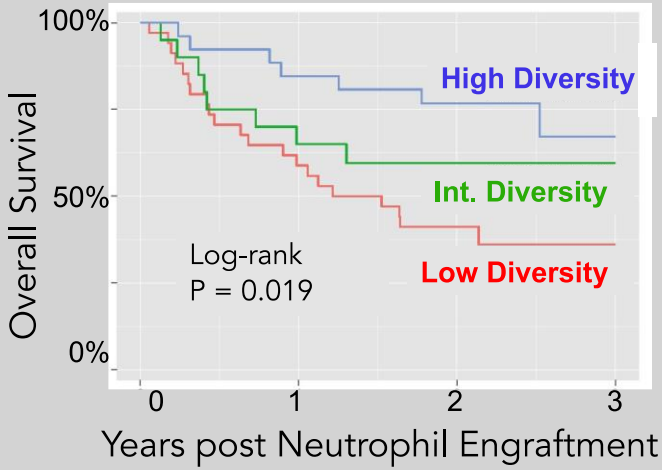
High Microbiota Diversity Predicts Survival and Protection from Acute GVHD

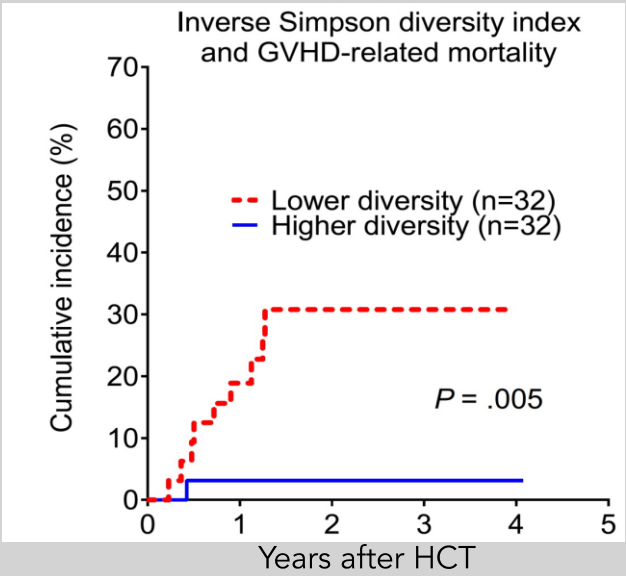
Overall Survival

sampled within 7 days post-engraftment



Taur, et al. *Blood* 2014, n = 80

Lethal GVHD



Jenq, et al. *BBMT* 2015, n = 64

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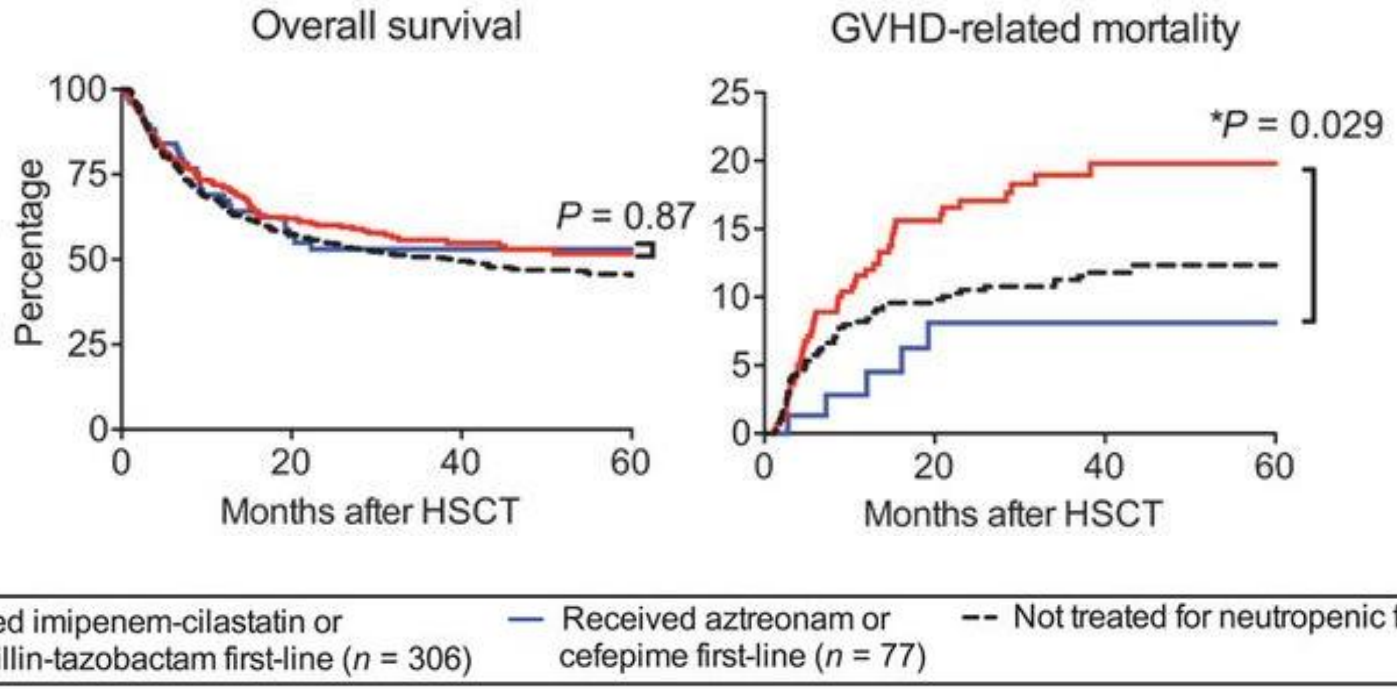
Antibiotics and Cellular Therapy

- Exposure to various medications has a differential impact on the intestinal microbiome (Nguyen CL, et al. *Cell* 2023).
- In particular, antibiotics disrupt the intestinal microbiome, a condition referred to as dysbiosis.
- Antibiotics, especially those aimed at obligate anaerobes (microorganisms that can't survive in the presence of oxygen), greatly impact these beneficial gut bacteria that play a crucial role in maintaining health.
- Obligate anaerobes play a crucial role in the immune response.
- Anaerobe-targeting antibiotics have also been linked to the responses to cellular therapy.

Anaerobic-targeting Antibiotics are Associated with Decreased Survival and GVHD Mortality



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Jenq, et al. *BBMT* 2015, n = 64

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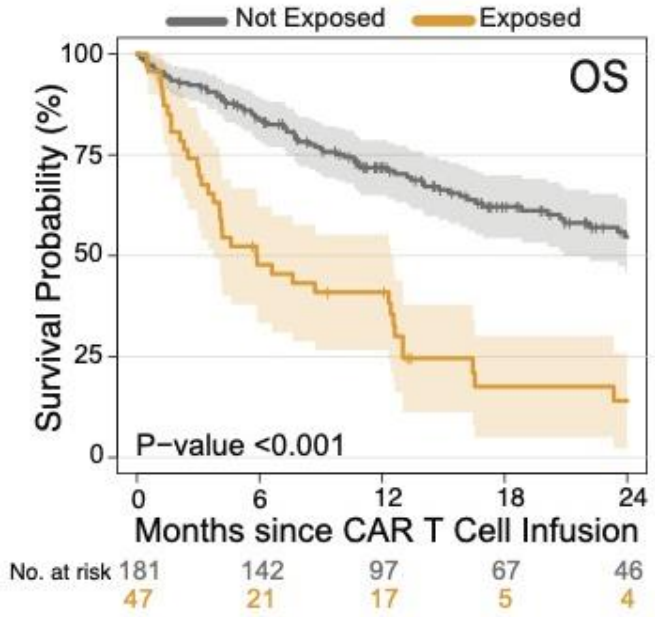
Anaerobic-targeting Antibiotics (PIM) Before CAR-T Infusion are Associated with Decreased Survival

Combined Malignancies: B-ALL, NHL



PIM: Piperacillin/tazobactam, Imipenem/cilastatin, and Meropenem

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Smith, M. et al. *Nat Med* 2022

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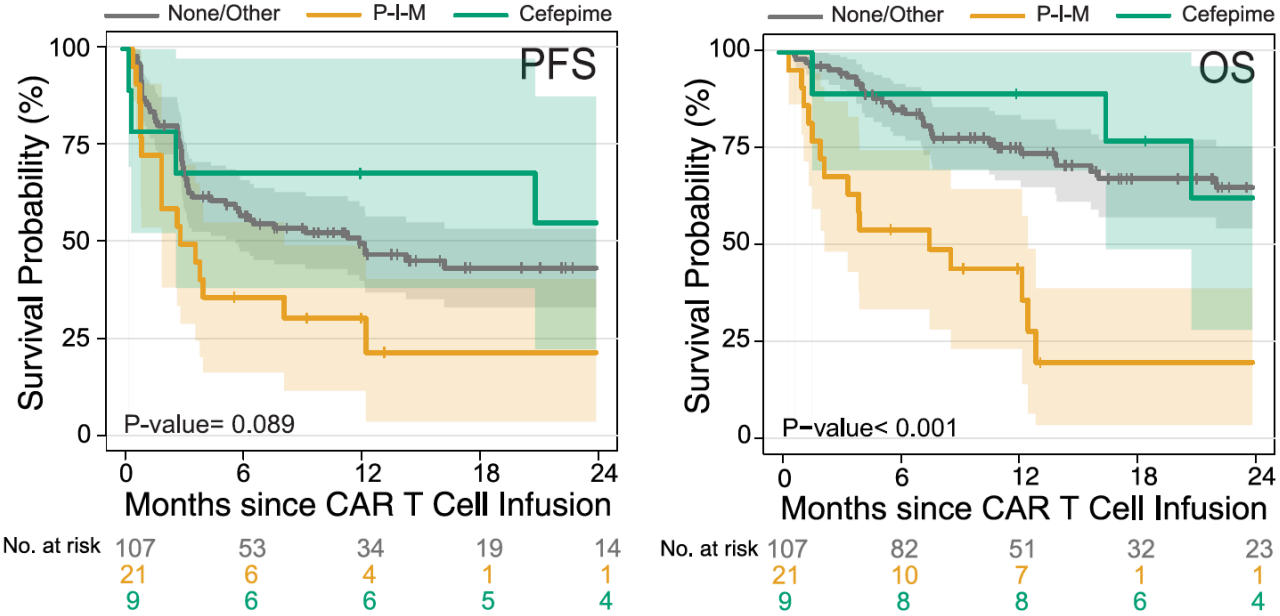
A Non-anaerobic-targeting Antibiotic (Cefepime) Before CAR-T Infusion is not Associated with Decreased Survival

Exposure to Cefepime



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Smith, M. et al. *Nat Med* 2022

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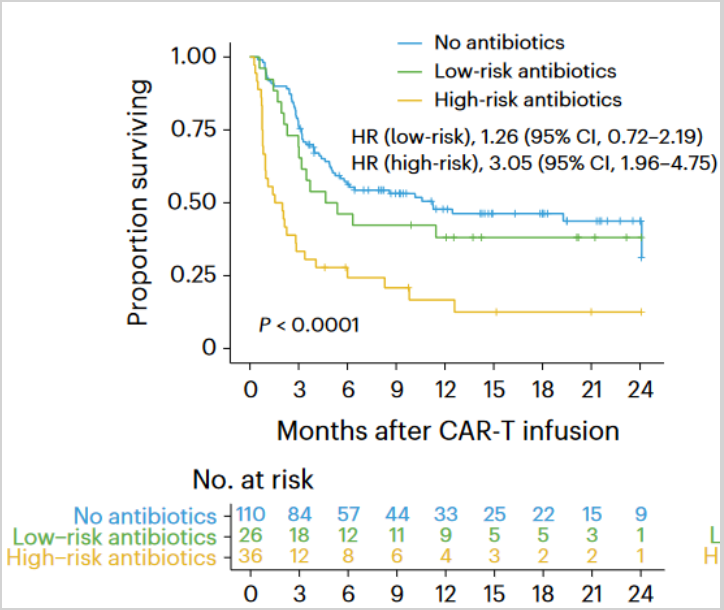
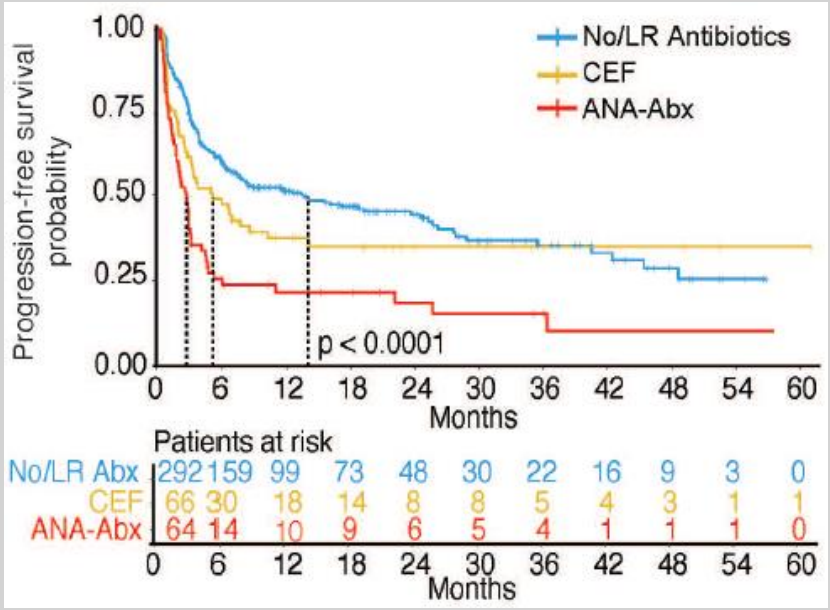
Anaerobic Antibiotic Exposure Before CAR-T Infusion is Associated with Decreased Survival



Stein-Thoeringer, C et al. *Nat Med* 2023



Prasad, R et al. *Blood* 2025

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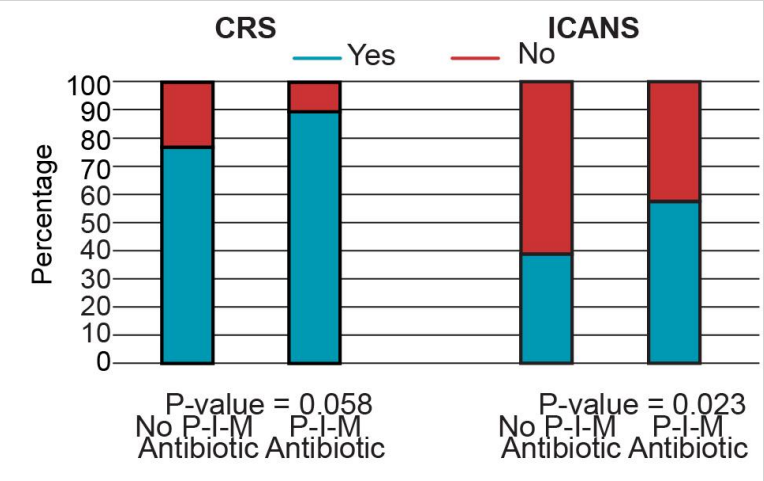
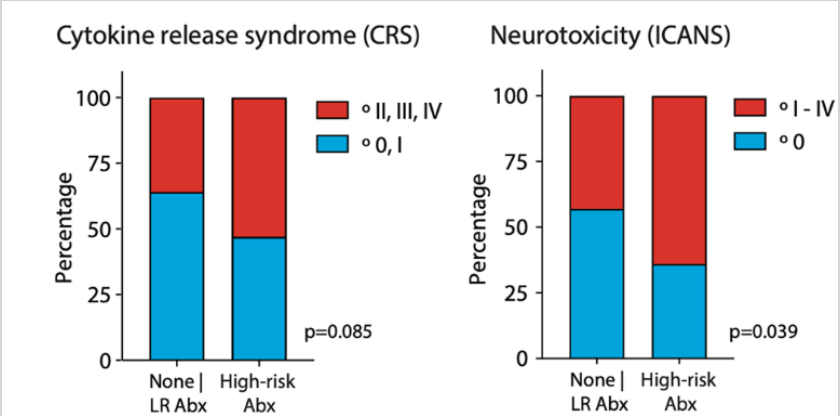
Anaerobic Antibiotic Exposure Before CAR-T Infusion is Associated with Increased ICANS



Smith, M et al. *Nat Med* 2022



Stein-Thoeringer, C et al. *Nat Med* 2023

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CRS=Cytokine release syndrome
ICANS=Immune effector cell-associated neurotoxicity syndrome

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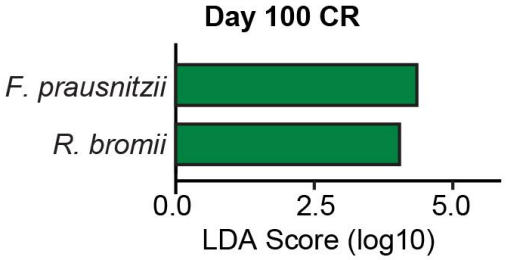
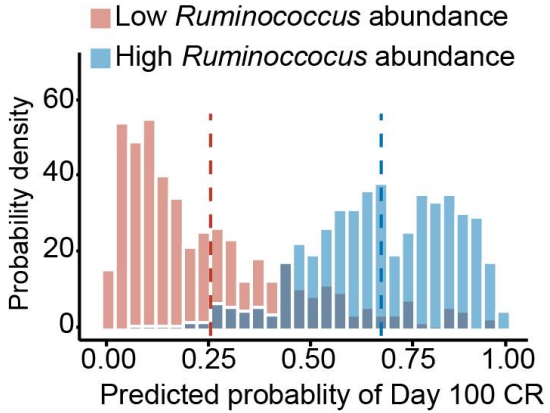
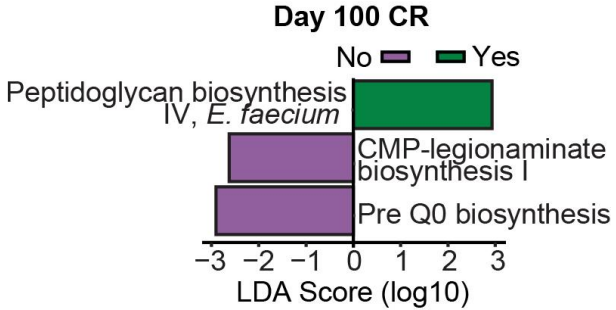
The Intestinal Microbiome is Associated with the Outcomes of CAR T cell Therapy

Pre-infusion samples







Specific bacteria and their metabolites (the compounds they produce) have been linked to how well patients respond to CAR T cell therapy.

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Smith, M. et al. *Nat Med* 2022

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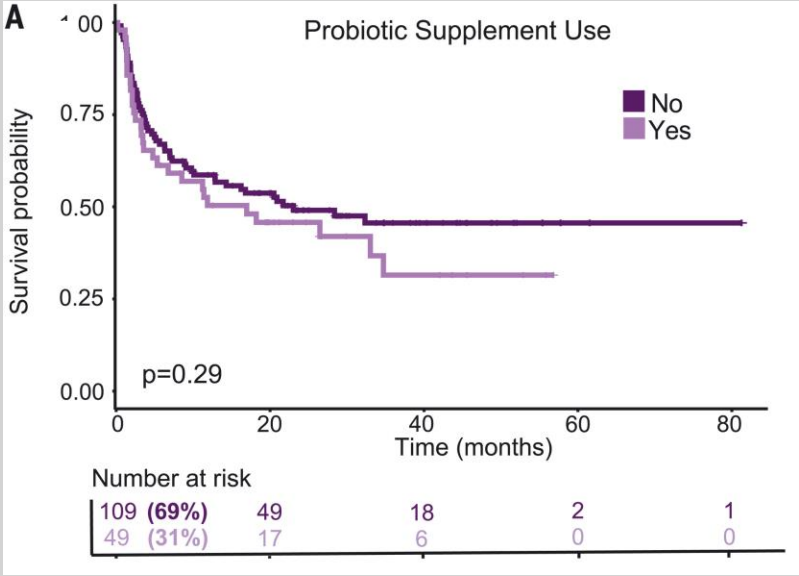
Summary II: Antibiotics and Cellular Therapy

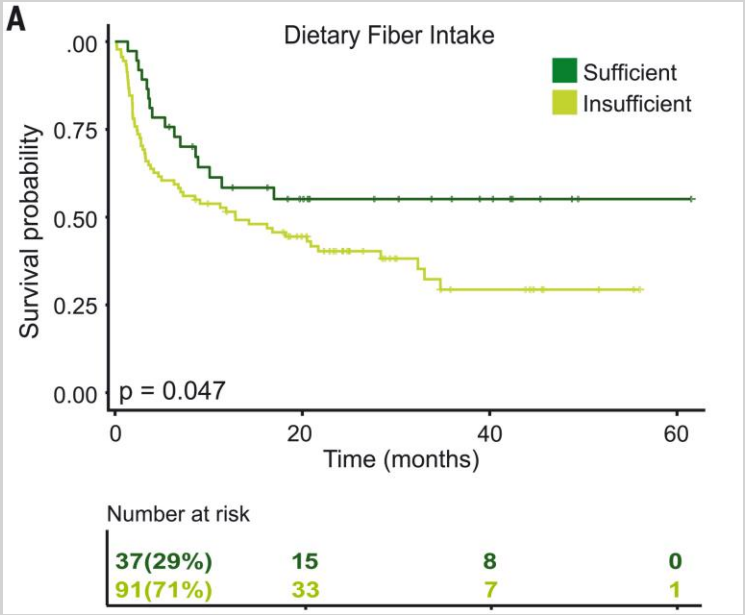
- Anaerobic-targeting antibiotic exposure during allo-HCT is associated with decreased survival and increased GVHD mortality.
- Exposure to anaerobic-targeting antibiotics in the weeks preceding CAR T cell therapy is linked to decreased survival and increased neurotoxicity.
- This data provides potential insights regarding antibiotic stewardship for clinicians caring for CAR-T and allo-HCT patients.
- Ongoing studies are investigating the mechanisms behind these antibiotic associations.

Objectives

- The role of the intestinal microbiome in outcomes following allo-HCT or CAR T cell therapy
- The impact of allo-HCT and CAR T cell therapy on the intestinal microbiome
- Interventions, including diet and lifestyle changes, that promote a healthy microbiome

Cancer Immunotherapy: Probiotics and High-Fiber Diet





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Spencer, CN. et al. *Science* 2021.

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Impact of Dietary Intervention on the Intestinal Microbiome

versus

36 adults were randomly assigned to a 10-week diet high in fiber versus fermented foods.

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Wastyk, HC. et al. *Cell* 2021.

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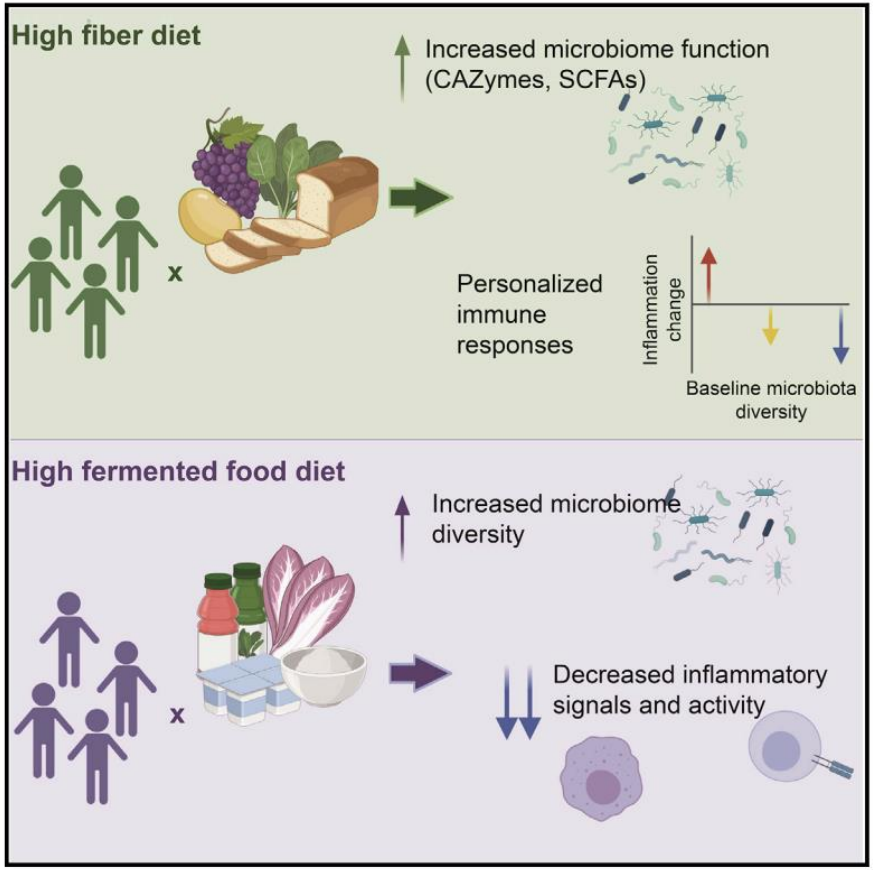
Fermented Diet Increased Microbiome Diversity More Than a High Fiber Diet



Wastyk, HC. et al. *Cell* 2021.

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Summary III: Interventions

- There is limited data on dietary interventions and cancer immunotherapy.
- However, extrapolation from other studies suggests that a diet in both fermented and high fiber foods promotes a healthy intestinal microbiome.
- There is no evidence to support the use of probiotics to improve the microbiome or clinical outcomes in this setting.

Acknowledgments

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River Joo
Sneh Patel

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Clinical Investigator Award

ASH Scholar

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K08 HL156082

nmdp
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Questions?

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