THE AVM TEAM: Revolutionizing the Future of Immunotherapy
For Refractory Lymphoma, Autoimmune Reset, and Preconditioning before CarT or Cell Therapy

*Theresa A. Deisher, Ph.D. / Founder & CEO*

Theresa A. Deisher, Ph.D. graduated from Stanford University School of Medicine with a doctoral degree in Molecular & Cellular Physiology. She has over 40 issued US/EU/JP patents and discoveries in clinic (Sprifermin Ph III, Factor XIII Ph II). She has had extensive scientific and management experience in the commercial biotechnology field including Genentech, Repligen, ZymoGenetics, Immunex/Amgen.

*Arya Ashok, Ph.D. / Scientific Program Director*

Arya Ashok has a doctorate from University of Maryland Baltimore County focused on Cancer Biology and Inflammation. At AVM, she leads internal research, external collaborations and manages AVM’s clinical trial programs.

*Peter Jarzyna, Ph.D. / Lab Director*

Dr. Peter Jarzyna received his PhD in pharmacy (tumor biology/imaging) from the University of Regensburg in Germany. He gained international experience in the field of preclinical cancer/imaging research and has successfully led multiple projects.

*Yumna Zahid, M.S. / Senior Research Scientist*

Ms. Zahid has experience in the fields of Stem Cell Biology and Immunology. She has previously worked in cell therapy research for Cystic Fibrosis and fibrosing diseases such as Idiopathic Pulmonary Fibrosis.

*Michael Anderson, MBA / President and Chief Administrative Officer*

Mr. Anderson has held key management and executive positions, including in the regulated banking industry and in manufacturing. Mr. Anderson joined AVM to build out the corporate infrastructure and the regulated clinical and commercial environment for successful launch of AVM0703 in relapsed/refractory lymphocytic blood cancers and refractory autoimmune disease.

*Neil O’Connor, MBA / Chief Financial Officer*

Neil O’Connor serves as AVM’s outsourced CFO from NOW CFO. He possesses over 20 years’ CFO expertise, gained across a variety of industries in organizations ranging from start-ups to $3++ multinationals.

*Terry Kopp / Vice President of Investor Relations*

Terrence Kopp had a 27-year successful history in marketing and sales with a major programming network in the cable TV. He has served in an investor relations leadership for AVM Biotechnology since 2014, including leading successful series B, C and D raises.

**AVM Consultants / Scientific & Clinical Advisory Board**

Dr. John Harlan, Chief Emeritus Hematology, Univ of WA; Dr. Gustavo Mahler, former CEO, AGC Biologics; Dr. Gordon Roble, Dir Comp. Med., Fred Hutch Cancer Res Ctr; Dr. Ed Loniewski, Advanced Orthopedic Specialists; Dr. Ann E. Woolfrey & Dr. Frank Smith, Medpace, Inc.
ABOUT LEAD DRUG AVM0703

• Data from our mouse studies have consistently demonstrated that:
  o AVM0703 is as effective against lymphoma and melanoma as chemotherapy
  o Anticipated toxicity/adverse events are transient and manageable
    (Chemotherapy killed 18% of mice while there is NO mouse death when treated with AVM0703 – Slide 7)
• AVM0703, with toxicology package, is ready for pivotal Adaptive Design, Master Protocol Clinical Trial in terminal/no option lymphoma. *
• Company will subsequently expand market to include autoimmune disease “immune reset” and replacing chemotherapy preconditioning in both oncology and regenerative medicine.
• As of May 31, 2019, we are anticipating first patient enrollment in a trial treating relapsed/refractory Non-Hodgkin Lymphoma (NHL) in the first half of 2020.

* The new FDA works with companies to approve new therapies for no-option patients (as early as 3 years and as little as 29 patients).
STEM CELL THERAPIES FOR REGENERATIVE MEDICINE HAVE LARGELY DISAPPOINTED CLINICALLY

PROBLEM IN EFFICACY:

The majority of patients do not respond to the stem cells because the patients were not pre-conditioned.
AVM0703 MAKES ANY STEM CELL WORK BETTER

REGENERATIVE MEDICINE PLATFORM
BONE MARROW TRANSPLANT TAUGHT US THAT INJECTED STEM CELLS FIRST HOME TO THE SPLEEN

Huge colonies of transplanted BM cells home to spleen and are visible by eye within 10 days

Spleens of irradiated mice 10 days after injection of $6 \times 10^4$ nucleated cells. Radiation Research 14, 213 - 222 (1961)

Cells recovered from the spleen engraft faster than bone marrow recovered cells

3 hours after injection into lethally irradiated recipients, 44% of BM cells can be found in the spleen

Secondary transplant of spleen recovered cells engrafted neutrophils 13 days faster than primary or secondary BM transplant.

Stem cell accumulation in the spleen is seen for bone marrow treatment just like accumulation for CAR-T/NK/TAC/TCR.


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**STEM CELL SEQUESTRATION IS A LIMITATION OF CELLULAR THERAPIES**

Stem cell homing to spleen and lymph nodes is a ubiquitous phenomenon

- The efficacy of cell therapies for both regenerative medicine and cancer is limited by short circulating half-lives and inefficient targeting of the cell therapies
- >90% of cells rapidly accumulate and remain in the spleen and lymph nodes
- This challenge exists for all cell types, all diseases and any route of administration

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**Cell Type:** Human Adipose MSC  
**Subject:** Rat  
**Delivery:** Intraocular/Striatal  
**Indication:** Biodistribution

**Cell Type:** Human Adipose MSC  
**Subject:** Human  
**Delivery:** IV Hand  
**Indication:** Arthritis/Biodistribution

**Cell Type:** Mouse ESC  
**Subject:** Mouse  
**Delivery:** Kidney Subcapsule  
**Transplant**  
**Indication:** Diabetes/Biodistribution (MRI)

**Cell Type:** Rat Bone Marrow MSC  
**Subject:** Rat  
**Delivery:** IV & IM  
**Indication:** Acute Myocardial Infarction

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Nereen Healthcare (2016)  
Barbash Circulation (2003)
EVEN CAR-T DISTRIBUTE TO SPLEEN, LIVER & LUNG

Ovarian cancer human α folate receptor CAR-T
Allo PBMC or IL-2 activated
No preconditioning
IV injection persisted in blood only 1 hour

Biodistribution of radiolabeled T cells


AML
TAA Lewis LeY CAR-T
Fludarabine 30 mg/m² day 1-5
CAR-T infused after BM recovery or 4 weeks later, at which time the spleen has recovered

Natural Killer cells also distribute to spleen & lymph nodes.

Ex vivo imaging of lethally irradiated allogeneic (BALB/c) and syngeneic (FVB/N) mice revealed NK accumulation in the spleens and mesenteric lymph nodes (mLN) of allogeneic (ALLO NK) and syngeneic NK (SYN NK) cell recipients.

Ex vivo imaging of RAG2-/- gammaC-/- mice revealed NK accumulation in the spleen and mLN, similar to lethally irradiated mice.
EVEN WITH INTRA-ARTICULAR INJECTIONS, MOST STEM CELLS DISAPPEAR FROM JOINT WITHIN 30 MINUTES

Both mares were injected with 5 to 7 million Dragon Green labeled allogeneic equine ADSC into both the carpus and tarsus joints.

Horse data presented here indicate that stem cells leave the knee joint rapidly.

Synovial tissue is highly vascularized
Unlike cartilage, synovium contains blood vessels, lymphatics and nerves.

Branching radial vessels from perimeniscal capillary plexus (PCP) penetrating peripheral border of the medial meniscus. (F) femur; (T) tibia.

Stem cells exit from the heart and accumulate in the spleen (red - viable) and liver (yellow –not viable).

Stem cell sequestration in the spleen is a universal phenomenon of stem cells and has been observed in multiple diseases. For example:

- Treatment of ischemic stroke patient with autologous bone marrow mononuclear cells (BMC).
- Direct injection to middle cerebral artery (MCA) – majority of stem cells migrate to the spleen.

*Barbosa da Fonseca LM et al. Circulation. 120:539-541 (2009)*

Chemokines from damaged organs are effective cell attractors, but only when the cells remain in the circulation, not in the spleen.

Chemokines from damaged organs increase stem cell targeting and retention (black columns post infarct; white columns sham). Retention is doubled by organ damage, whether the stem cells are administered intravenously or injected directly into the damaged organ (intracavitary). However, unless spleen binding is blocked less than 5% of cells will be retained in target.

*Circulation. 2003 Apr 29;107(16):2134-9*
AVM DISCOVERS STEM CELL BINDING NICHES

AVM is the first to identify the stem cell binding niches in the spleen and secondary lymphatics

- AVM0703 pretreatment prolongs circulating half-life of cell therapies by safely lymphodepleting & selectively eliminating the sites in the spleen where stem cells and cellular immunotherapies rapidly accumulate

- Broad issued and pending patent claims covering any molecule that inhibits cell binding in lymphoid tissues to augment the numbers of circulating cells

Co-labeling of spleen niche (green) and stem cells (red)
AVM0703 ELIMINATES STEM CELL BINDING SITES IN THE SPLEEN

**Control** vs. **AVM0703 Medium Dose**

**Control**: Average of either not injected (n=5 C57BL/6; 4-5 slices per mouse; sacrificed after 96 h). Error bars: SEM

**AVM0703** administered (n=4 C57BL/6 mice; 4 to 5 slices per mouse; sacrificed after 96 h)

**AVM0703 decreases stem cell binding sites**

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THE PROBLEM - CURRENT AVAILABLE PRECONDITIONING TREATMENTS ARE TOO TOXIC AND TOO COSTLY

Preconditioning Before Cell Therapies

Preconditioning is required before any cell therapies

Unfortunately, 30-50% of patients are too frail or refractory for chemotherapy preconditioning and do not qualify for CarT treatment.

Autoimmunity, Allergy & Asthma

Alternative treatment options limited

The only curative treatment for Autoimmune diseases is toxic high-dose chemotherapy to “immune reset”.

Medical management after chemotherapy is costly

Adverse effects from CarT cause Cytokine Release Syndrome (CRS) and neurotoxicity. These toxicities can add $20,000-$60,000 per patient to total treatment cost. (Leukemia and Lymphoma Society Factsheet 2018)

Continued decline in health leads to escalating chronic care, increasing cost and decrease quality of life

Because chemotherapy ‘immune reset’ is so toxic, the majority of patients choose to take life-long low-dose chemotherapy with its own toxicities or use biologic drugs (Humira, Enbrel and Remicade).
AVM0703 BLOCKS STEM CELL BINDING IN THE SPLEEN, KEEPING STEM CELLS IN THE BLOOD, MEASURED BY WHOLE BLOOD CFU-GE Hamm

CFU-GE Hamm OF LYSED WHOLE BLOOD
(200,000 CELLS/ML - 6 WELL PLATE)

AVM0703 was administered concomitantly with two doses of Neupogen® (n=4 C57BL/6 mice per group; sacrificed after 96 h).

The graph on the left shows that AVM0703 keeps G-CSF mobilized stem cells in the blood.

AVM0703 INHIBITION OF STEM CELL SEQUESTRATION IN THE SPLEEN (MICE N=4)

AVM0703 EFFECT ON STEM CELL NUMBER IN WHOLE BLOOD (MICE N=4)

AVM0703 blocks stem cell binding in spleen.

AVM0703 increases systemic stem cell circulation.
Medium-High AVM0703 DOSE REDUCES NK AND T-CELL SEQUESTRATION IN Spleen

**NK Cell Intensity Binding to Spleen**
- Vehicle: [Graph]
- AVM0703: [Graph]

**% of spleen Area Bound**
- Vehicle: [Graph]
- AVM0703: [Graph]

**Naive T Cell Intensity Binding to Spleen**
- Vehicle: [Graph]
- AVM0703: [Graph]

**% of spleen area bound * Spl/BW**
- Vehicle: [Graph]
- AVM0703: [Graph]

Vehicle treated NK cell binding

Treated w/ Medium-high AVM0703

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One week after bone marrow concentrate (BMC) infusion, cells are still found in the spleen.

With AVM0703 pre-treatment, cells did not accumulate in the spleen. Therefore, there are more viable stem cells in circulation that are available to be chemo-attracted into damaged organs.
Mesenchymal Stem Cell (MSCs) numbers were measured as colony forming units – fibroblasts (CFU-F). Hematopoietic Stem Cell (HSCs) numbers were measured by CFU-GEMM (Granulocyte, Erythrocyte, Monocyte, Megakaryocyte)
AVM0703 INCREASES BONE MARROW CFU-F IN HORSES BUT DOES NOT IMPACT MESENCHYMAL STEM CELL (MSC) FUNCTION

Administered as one-hour IV infusions, AVM0703 expected acute adverse responses were eliminated. No chronic toxicities have been observed for out to 3 years after treatment.

AVM0703 non-significantly increased MSCs in the bone marrow and is safe to use.

AVM0703 does not change MSC capacity to differentiate to cartilage (chondrocyte), bone (osteocyte) or fat (adipocyte)-producing cells.

*MSC is determined by Colony Forming Unit-Fibroblast (CFU-F) assay

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Low dose AVM0703 may increase Bone Marrow CFU-F per ml compared to 31 historical controls aspirated using the same needle as for Patients M & P.

2 of 4 patients had BM aspirated with a special concentrating needle.

Both patients had CFU-F counts higher than naïve patients aspirated using the same needle.

This is similar to observations in horses treated with medium-low dose AVM0703 on the previous slide.

*4 patients were treated in our study. Lymphodepletion data below is only shown for 3 patients because one did not have the CBC* performed to calculate absolute numbers. *CBC: Complete Blood Count

Below is an increase in IL-2 and IL-15 cytokines after 48 h post-treatment with AVM0703, which is similar to the cytokine profile of chemotherapy.*

*All 4 patients showed elevated cytokine levels.

**HUMAN CYTOKINES: PRE versus POST (48H) AVM0703**

**PROCARTPLEX-LUMINEX ASSAY**

*p ≤ 0.05 (pre vs post)
Stem cell homing in spleen and lymph nodes is a ubiquitous phenomenon. It is independent of type of stem cell, route of administration and disease. Moreover, the bound cells are long-term and viable cells.

AVM technologies control this by blocking stem cell homing to the spleen and lymph node, enabling stem cells to remain longer in circulation and to home in greater numbers to sites of injury or damaged organs.

When the stem cells are bound in the spleen and lymph nodes they cannot respond to chemokines like SDF-1 that damaged organs are producing. AVM0703 keeps the stem cells in the blood where they are able to respond to SDF-1 and other chemokines.

With chemotherapy spleen cellularity is obliterated and CAR-T remain in blood

CD19+ relapsed malignancies
CD19 CAR T
Bendamustine 1-3 cycles 7 days before CAR T
or Pentostatin/cyclophosphamide UPN03
CAR T infused immediately after bendamustine cycle


Each line in the graph represents one patient.
Chemotherapy preconditioning allowed the CarT
to remain in the circulation for 180 days of observation.

AVM0703 could replace chemotherapy preconditioning, keeping CAR T cells in the circulation without the toxic side effects of chemotherapy.
THE SOLUTION - AVM0703 ELIMINATES TOXICITY AND DECREASES EXPENSES, THUS RESTORING QUALITY OF LIFE

ELIMINATE
Toxic Chemotherapy

CURE
Autoimmune Diseases by Immune-reset

RESTORE
Patients’ Quality of Life
AVM0703 LYMPHO- AND MONO-ABLATION FOR RELAPSED/REFRACTORY LYMPHOCYTIC BLOOD CANCERS, IMMUNE RESET FOR AUTOIMMUNE DISEASE, AND REPLACEMENT OF CHEMOTHERAPY/RADIATION PRECONDITIONING BEFORE CAR-T OR CELL THERAPY

AVM0703 selectively ablates T and B lymphocytes (equivalently to standard Cy (2X)/Flu 4X)) and monocytes (superior to Cy/Flu), and lymphodepletes neutrophils at the target clinical dose. Basophils (reduced only at the 6 hour time point) and eosinophils (reduced only at the 24 and 48 hour time points), platelets, & RBCs are spared, and HSC & MSC are spared or increased. (* p < 0.05; # p < 0.0001)
AVM0703 REDUCES TARGETED CELLS WITH FASTER RECOVERY THAN CHEMOTHERAPY

We have data in mice, rats and human osteoarthritis patients.

Mouse Data

![Graphs showing lymphocytes, monocytes, and neutrophils with recovery times and reductions](https://example.com/graphs.png)
AVM0703 DRAMATICALLY IMPROVES THE EFFECTIVENESS OF CarT CELLS IN A MELANOMA MODEL

AVM0703 also delayed melanoma tumor growth equivalently to 20M pmel CarT cells (female donor) and, used as a preconditioning agent, significantly improved melanoma response to pmel CarT cells. Higher AVM0703 doses were equivalent to Cy preconditioning in the Mouse B16F10 Melanoma Model when CarT pmel cells from male donor mice were used.

B16F10 melanoma cells are inoculated on day -9. Pre-conditioning is done on day 1 with low dose AVM0703 or on day 2 with 13 mg /kg HED Cyclophosphamide. Adoptive transfer of 20M transgenic CD8+ cells expressing the anti-gp100 TCR from pmel-1 mice is done on day 3. Tumor volumes are measured by calipers. A single dose of AVM0703 is as effective as 20M pmel cells to delay tumor growth. AVM0703 and Cy pre-conditioning before 20M pmel cells both significantly delay tumor growth compared to 20M pmel cells alone and compared to their use alone.
AVM0703 can be combined with Cy/Flu to reduce the total Cy/Flu dose with equal efficacy against lymphoma compared to repeat Cy/Flu or CHOP treatments.

AVM0703 + 1 dose Cy/Flu (chemotherapy) delays A20 mouse lymphoma growth as well as 2 cycles of CHOP.

CHOP tumor volumes are from Bascuas 2016. Two doses of CyFlu on day 11 and day 14 (HED 13.6 mg/kg and ) have completely eradicated A20 tumors in all mice by day 32 after A20 inoculation. AVM0703 can replace the first CyFlu dose on day 11 and completely eradicate A20 tumors in all mice by day 32 after inoculation. Mice will continue to be followed to determine if tumors relapse.
**RED BLOOD CELLS AND PLATELETS ARE SPARED REDUCING NEED FOR TRANSFUSIONS**

*Mouse Data*
INTRIGUINGLY, AVM0703 INDUCES NKT UPREGULATION, POTENTIALLY PROTECTING PATIENTS FROM NEOPLASTIC ESCAPE OR AUTOIMMUNE ADVERSE EVENTS

Chemotherapy does not upregulate NKT
LYMPHOABLATION CAN CURE AUTOIMMUNITY. COMPARED TO CHEMO, AVM0703 SPEEDS RECOVERY AND ELIMINATES POST-TREATMENT TRANSFUSIONS AND INFECTIONS, SPARES PMNS, PLTS, RBCS AND HSCS.

<table>
<thead>
<tr>
<th>CD4 Nadir*</th>
<th>22 cells per μL</th>
<th>115 cells per μL</th>
<th>155 cells per μL</th>
<th>25 cells per μL</th>
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<tbody>
<tr>
<td>CD8 Nadir</td>
<td>50 cells per μL</td>
<td>172 cells per μL</td>
<td>464 cells per μL</td>
<td>1.4 cells per μL</td>
</tr>
<tr>
<td>B Lymphs Nadir</td>
<td>12 cells per μL</td>
<td>30 cells per μL</td>
<td>97 cells per μL</td>
<td>58 cells per μL</td>
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<tr>
<td>Time to Lymphocyte Recovery</td>
<td>&gt;6 months</td>
<td>&gt;1 year</td>
<td>&gt;9 months</td>
<td>7-14 days</td>
</tr>
<tr>
<td>Disease Relapse</td>
<td>17% at 66 mos (5.5 yrs)</td>
<td>~70% within 10 months</td>
<td>~ 50% under 3.5 years</td>
<td></td>
</tr>
</tbody>
</table>

*Madir: the lowest point in any continuously measured lab test
AVM0703 WIPES OUT ALL LYMPHOCYTE COMPARTMENTS, WHICH CAN CURE AUTOIMMUNE DISEASES

AVM0703 can safely reduce lymphocytes essentially to ZERO, which is the goal to cure autoimmune diseases.

AVM0703 induces new NKT cells

Peripheral Blood Lymphoablation
Absolute Lymphocytes minus NK and NKT cells

Natural Killer & Natural Killer T cells

Spleen Lymphoablation
Spleen Weight to Body Weight Ratio

Thymus Lymphoablation
Thymus Weight to Body Weight Ratio

Spleen is 50% white blood cells/white pulp and spleen weight is reduced 50% for lymphoablation

Thymus
Lymphoablation

Mouse Data
HUMAN LYMPHODEPLETION STUDY USING LOW DOSE AVM0703
AVM0703 INCREASES PLASMA IL-2 & IL-15, BUT DOES NOT INCREASE IL-6

AVM0703 increased plasma IL-2 and IL-15 equivalently to multi-day cytotoxic Cy/Flu chemotherapy (comparison results for Cy/Flu are shown below). Most importantly, with AVM0703, IL-6 levels did NOT increase. Cy/Flu increases in IL-6 trigger sometimes fatal CRS.

**These 3 graphs are taken from Kite Pharma’s US patent 9855298 B2 where multiday Cy/Flu preconditioning was given to patients.**
With low dose AVM0703, only Patient P and Patient K responded. Medium and high dose studies are being planned. *

*4 patients were treated in our study. Lymphodepletion data below is only shown for 3 patients because one did not have the CBC measured so that absolute numbers could be calculated for flow cytometry results.

**HUMAN LYMPHOEDEPLETION USING LOW DOSE AVM0703**

Low dose AVM0703 spares the patients’ neutrophils and platelets. It means that AVM0703 has the potential to protect patients from possible infections. *

*Only 2 of 4 patients (Patient P & K) responded to 3mg/kg dose with lymphodepletion.

**ABSOLUTE CD3+ (N=3)**

**ABSOLUTE CD4+ (N=3)**

**ABSOLUTE CD8+ (N=3)**

**HUMAN CBC*: NEUTROPHILS**

**HUMAN CBC*: LYMPHOCYTES (N=3)**

**HUMAN CBC*: PLATELETS**

*CBC: Complete Blood Count

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PHARMACOLOGY AND PHARMACOKINETICS

No difference in horse vitals between placebo and AVM0703-treated groups (n=8 per group)

Expected elevations in cardiac and respiratory rates can be eliminated by oral administration or slow 1 hour IV infusion

![Graph showing pulse rate and respiratory rate before and after treatment with placebo and AVM0703.]
AVM HAS A SUBSTANTIAL WORLDWIDE PATENT PORTFOLIO

CODE FOR PATENT STATUS
- **Granted**
- **Under Examination**

Additional Patents Filed as of Nov 2018:
- Method patent for standalone uses of AVM0703
- Composition of Matter Patent
# Optimal Preconditioning Profile

<table>
<thead>
<tr>
<th>No Bone Marrow Redistribution</th>
<th>CY/FLU</th>
<th>AVM0703</th>
<th>TEMODAR, RITUXIMAB, ETC</th>
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<tr>
<td>Deplete Peripheral Blood Lymphocytes</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
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<tr>
<td>Decrease ACT Binding in Spleen</td>
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<td>✔️</td>
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<tr>
<td>Decrease Thymocytes</td>
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<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Increase in IL-2, IL-7, IL-12 and IL-15</td>
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<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>No Increase in IL-6 or GM-CSF</td>
<td>✗</td>
<td>✔️</td>
<td>✗</td>
</tr>
<tr>
<td>Spare Plts, RBCs, Stem Cells, Epithelial Cells and Endothelial Cells</td>
<td>✗</td>
<td>✔️</td>
<td>✗</td>
</tr>
<tr>
<td>No CRS, neuroedema, angioedema, fatal infusion reactions</td>
<td>✗</td>
<td>✔️</td>
<td>✗</td>
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</tbody>
</table>