Cincinnati Children’s Hospital

Bone Marrow Transplantation In Fanconi Anemia

Stella Davies, Parinda Mehta, Kasiani Myers and Richard Harris
The Bone Marrow Makes All the Cells in the Blood

- Red blood cell
- White blood cells
- Platelets
Bone Marrow Stem Cells

• Bone marrow grows from stem cells that live in bones.

• We can collect stem cells from the bones with needles, just like when your child has a bone marrow test.

• Stem cells are like seeds.

• Stem cells can grow a whole new bone marrow in a different person over time.
Chemotherapy or radiation removes child’s diseased bone marrow

10 Days

Stem cells collected and infused; starting to grow

30 Days

Complete new bone marrow

1 Year
Will my child need a transplant?

• Most children with FA develop low blood counts at some time—the most common age for this to start is around 5-8 years old, but some children have normal counts for much longer.

• Transplant is not needed right away if low counts are mild. Mild means not needing blood or platelet transfusions and no serious infections.

• When marrow failure is severe enough to cause infections or need transfusions, or there are signs of malignancy in the bone marrow is the time to think about transplant.
Why do different children need transplants at different ages?

- Mutations in many different genes can cause FA.
- Children with mutations in different genes will get marrow failure at different ages.
- Brothers and sisters who have the same mutations may need transplant at very different ages; things in the environment, or illnesses like viruses may affect how well the marrow works.
Can we do anything to help prevent my child from needing a transplant?

• Children develop marrow failure because the marrow stem cells die (production of blood cells can’t go on if there are no stem cells).

• The marrow stem cells die because children with FA have high levels of a protein called TNF that kills the stem cells by making ROS (reactive oxygen species).
Removing ROS Might Preserve Marrow Stem Cells and Prevent Marrow Failure in Fanconi Anemia

• We have tested a food supplement that can reduce ROS in laboratory mice who have Fanconi anemia
Food Supplement Prevents Leukemia in Mice With Fanconi Anemia

• Cells from Fanconi mice do not turn into leukemia cells after treatment with this food supplement.

• Children and mice with Fanconi anemia have “pre-diabetes”- this food supplement also makes this better.
Study of Food Supplement in Fanconi Anemia

• Our study of the food supplement in children is now open
• This food supplement has been studied in adults with other diseases and no side effects were seen.
• First three people enrolled need to be 12 years of age or older
• After that, anyone over 2 years old can enroll.
Study of Food Supplement in Fanconi Anemia

• We will measure levels of the food supplement in the blood to see if we can get the same levels we used in the mice.
• The food supplement is a liquid and is taken twice a day.
• We will follow blood counts, growth and blood sugars closely to see the effects of the supplement.
What if my Child Does Need a Transplant?

• Transplant is easiest if a brother or a sister is an HLA match.

• “HLA” are proteins on the surface of a cell that identify who it belongs to.

• There is a one in four chance that any brother or sister will be an HLA match to each other.
What Can We Expect if Our Child Has a Matched Sibling Donor?

• Dr Harris has reviewed the 35 sibling donor transplants for FA performed in Cincinnati.

• 25 boys/10 girls

• Ages 2.7-22.9 years

88% of those children (almost 9 out 10) are alive and well with normal blood counts 10 years later; all the children transplanted in the last 15 years are surviving.
What Can We Expect if Our Child Has a Matched Sibling Donor?

• In the past children receiving transplants from siblings have been treated with radiation.
• Children with sibling donors now do not receive radiation to reduce the risk of later cancers and other side effects.
What Can We Expect if Our Child Does Not Have a Matched Sibling Donor?

• Unrelated donors are volunteers who have agreed to be tissue typed in case they match someone who needs a transplant.

• The tissue types are stored in a large computer belonging to the National Marrow Donor Program.

When a donor is needed, your child’s tissue type is entered into the computer to see if there is a match—called running a search.
Finding an Unrelated Donor: Bone Marrow Registries

• There are almost 9 million unrelated donors in the US registry.

• We also look for donors in registries in other countries via the internet; we are all linked -19 million donors worldwide.

• Donations are anonymous; you don’t know who your donor is until at least a year after a transplant.
Umbilical Cord Blood Contains Bone Marrow Stem Cells

- Cord blood doesn’t have to be as well matched as marrow so can be a choice for children who need a transplant and can’t find a match in the registry.
- 500,000 cord bloods are frozen in banks worldwide.
Unrelated Donor Transplantation: What Should We Expect?

• Currently 4 transplant centers are working together to figure how we can get rid of radiation for unrelated donor transplants too: the FA Multi-center study

• Supported by FARF and Dr Eva Guinan
Unrelated Donor Transplant Without Radiation: FA Multi-Center Study

• Radiation increases the risk of later cancers and other side effects.
• This protocol uses a medicine called busulfan instead of radiation.
• Levels of busulfan are measured and adjusted to the individual so they do not get too high.
## Unrelated Donor Transplant Without Radiation

<table>
<thead>
<tr>
<th>Center</th>
<th>No. of Transplants</th>
</tr>
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<tbody>
<tr>
<td>Cincinnati</td>
<td>20</td>
</tr>
<tr>
<td>Sloan Kettering (New York)</td>
<td>5</td>
</tr>
<tr>
<td>Boston</td>
<td>2</td>
</tr>
<tr>
<td>Wisconsin</td>
<td>1</td>
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# FA Multi-Center Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number</th>
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<tbody>
<tr>
<td>Age Range</td>
<td>4.3-31.4 years</td>
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<tr>
<td>Age – Median*</td>
<td>8.1 years</td>
</tr>
<tr>
<td>Gender</td>
<td>14 males 14 females</td>
</tr>
<tr>
<td>Marrow at Transplant</td>
<td>22</td>
</tr>
<tr>
<td>Marrow failure</td>
<td>6</td>
</tr>
<tr>
<td>Marrow failure Marrow failure</td>
<td></td>
</tr>
<tr>
<td>Marrow failure Marrow failure pre-leukemia</td>
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</table>
## FA Multi-Center Study

<table>
<thead>
<tr>
<th>Donors</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matched unrelated</td>
<td>16</td>
</tr>
<tr>
<td>Mismatched unrelated</td>
<td>5</td>
</tr>
<tr>
<td>Related (non sibling; mostly parents)</td>
<td>6</td>
</tr>
</tbody>
</table>
FA Multi-Center Transplant Study

- 28 persons enrolled; 24 are surviving
- 4 have died, 3 of infection and one of side effects of the treatment.
- The study first enrolled 25 patients to see if busulfan worked well.
- Next 10 are being treated with a lower dose of busulfan and currently that is going well (3 treated at lower dose so far).
- The 10 children treated after that will get an even lower dose of busulfan.
Conclusions

• A new study of a food supplement is open and we hope it will help delay the counts going low in people with Fanconi Anemia.
• Transplant generally turns out well if there is a brother or sister who can be a donor.
• Most children who do not have a matched brother or sister will find a donor in a registry, or we can use cord blood or even a Mom or Dad as a donor.
• Results of these transplants are getting much better, and we no longer need to use radiation for the transplant.