

The New Protocol

Risk-Adapted Radiation-Free Transplant For Fanconi Anemia



Fanconi Anemia

Age less than 18

Age more than 18

Bone marrow failure

MDS or AML

Bone marrow failure

MDS or AML

Busulfan
0.6mg- these patients did very well on current study with this dose

Busulfan
0.8mg – higher dose to better prevent relapse

Busulfan 0.4 mg- older patients have more side effects and may do better with lower dose

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Post-transplant azacytidine maintenance to prevent relapse

Risk-Adapted Protocol

- Open in Cincinnati, opening shortly in New York
- Three patients enrolled, one adult with AML, one adult with MDS and one younger child with marrow failure.
- All currently doing well.

Can We Prevent Marrow Failure and Leukemia?

Quercetin, a food supplement that prevents leukemia in mice with Fanconi Anemia.

Reactive Oxygen Species (ROS) in FA

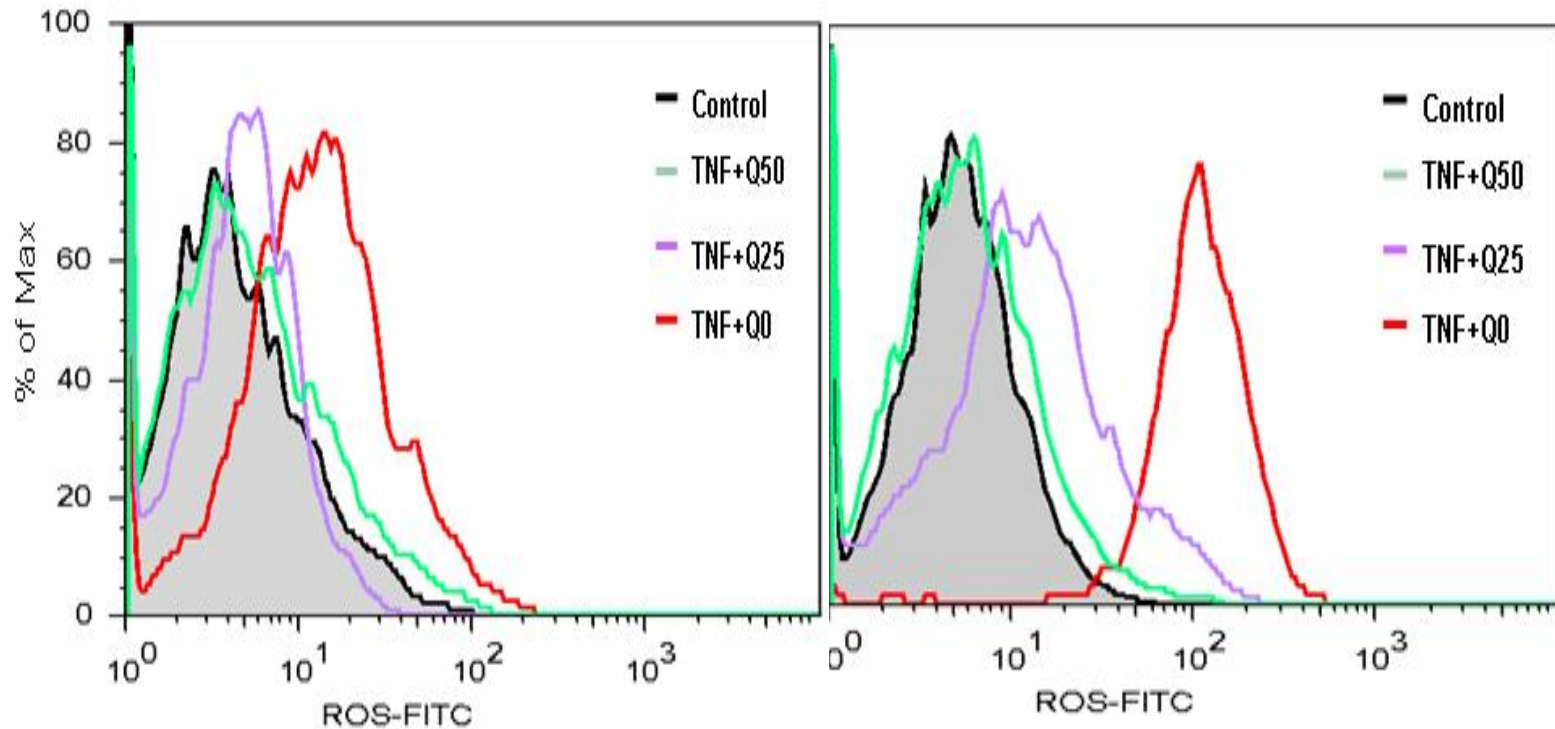
- Mice and humans with FA have high levels of reactive oxygen species in the bone marrow and we think this causes marrow failure and leukemia.

Quercetin prevents marrow failure and leukemia in Fanconi mice

- Quercetin improves the stem cell compartment – increases cells that make blood cells in mice with FA
- Cells from Fanconi mice do not turn into leukemia after treatment with Quercetin



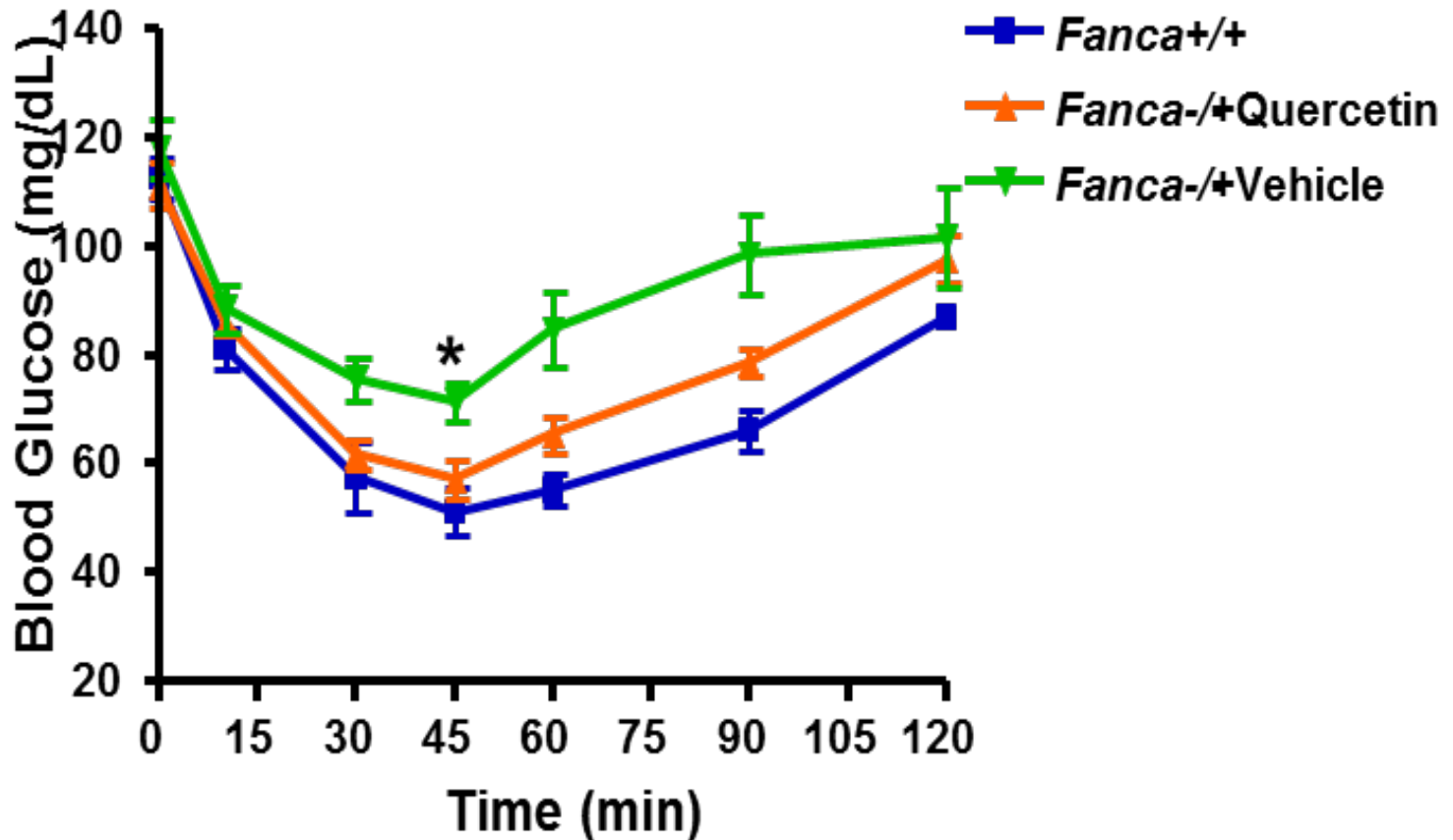
Quercetin (antioxidant) reduces TNF-generated ROS



Normal Control

FA-A

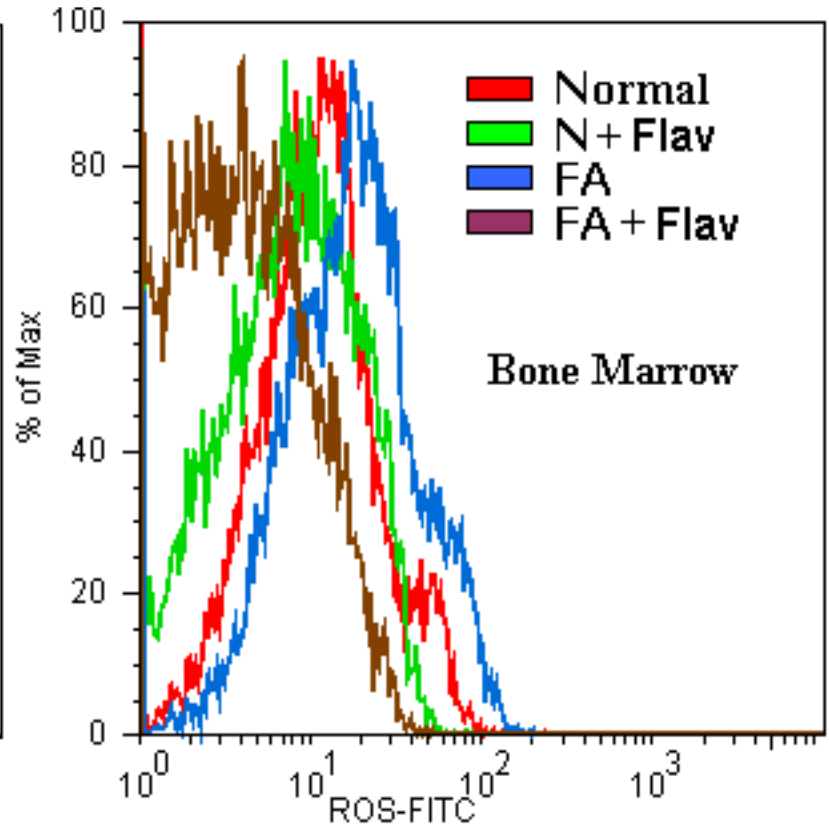
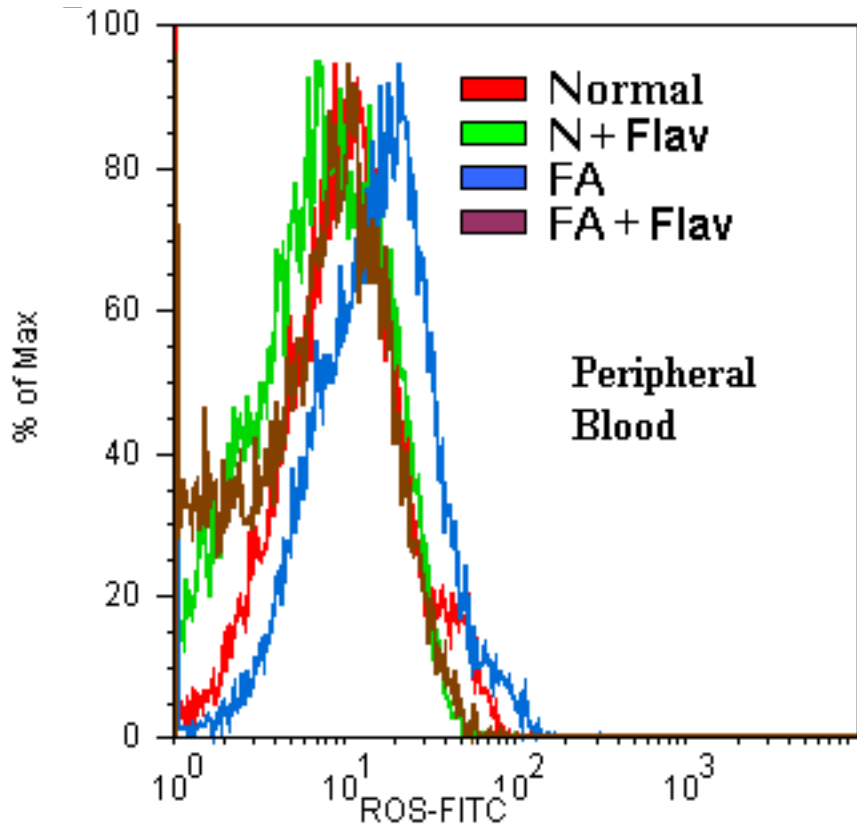
Mice with Fanconi anemia have “pre-diabetes” (similar to children with FA)
– quercetin also makes this better



So, what happens in patients?

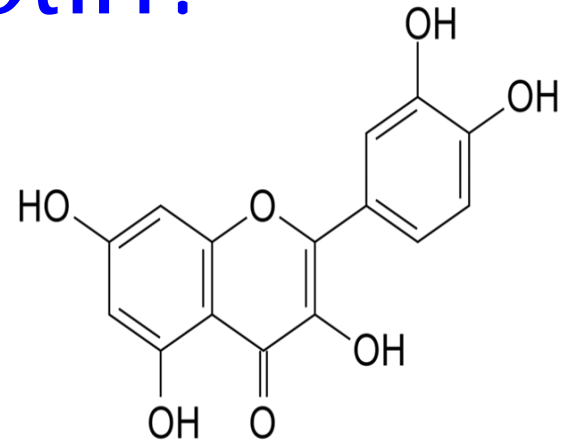
- Patients with FA produce increased ROS levels compared to normal controls
- ROS levels decrease to baseline with addition of Quercetin in laboratory studies, using both bone marrow or peripheral blood samples from patients with FA

Reversal of ROS with Quercetin in patients with FA



What is Quercetin?

- Quercetin (3, 30, 40, 5, 7-pentahydroxyflavone) is a naturally occurring flavonoid
- Richest dietary sources include onions, apples, berries, tea and red wine
- Common ingredient in dietary supplements and multivitamin preparations



Clinical trial of Quercetin in patients with FA

- Our study of Quercetin in patients with FA is now open and enrolling

Clinical trial of Quercetin in patients with FA

Three goals:

1. Establish safety
2. Establish feasibility of long term administration: can children really take it twice a day for long periods of time?
3. Obtain pharmacokinetic data/drug level – making sure we can get good levels of quercetin in the blood of FA patients so they get the benefits we see in the mice.

Quercetin in FA

- This study will enroll 12 patients in different stages of marrow failure

Inclusion Criteria

- Diagnosis of FA proven by DEB test
- Able to take medication by mouth

Major Exclusion Criterion

- Patients with myelodysplasia or leukemia

Quercetin Administration

- Quercetin is supplied as a liquid suspension, to be taken twice a day
- Quercetin has no real flavor, and is a cheerful yellow color
- Patients are treated with Quercetin twice a day for **4 months**

Monitoring for safety and feasibility of Quercetin in FA patients

Patients are monitored closely for any side effects:

- Weekly phone calls from study co-ordinator
- Pre-treatment testing, regular blood tests
- Follow up visit with bone marrow testing at 4 months and again at 1 year
- Blood glucose testing before and after quercetin

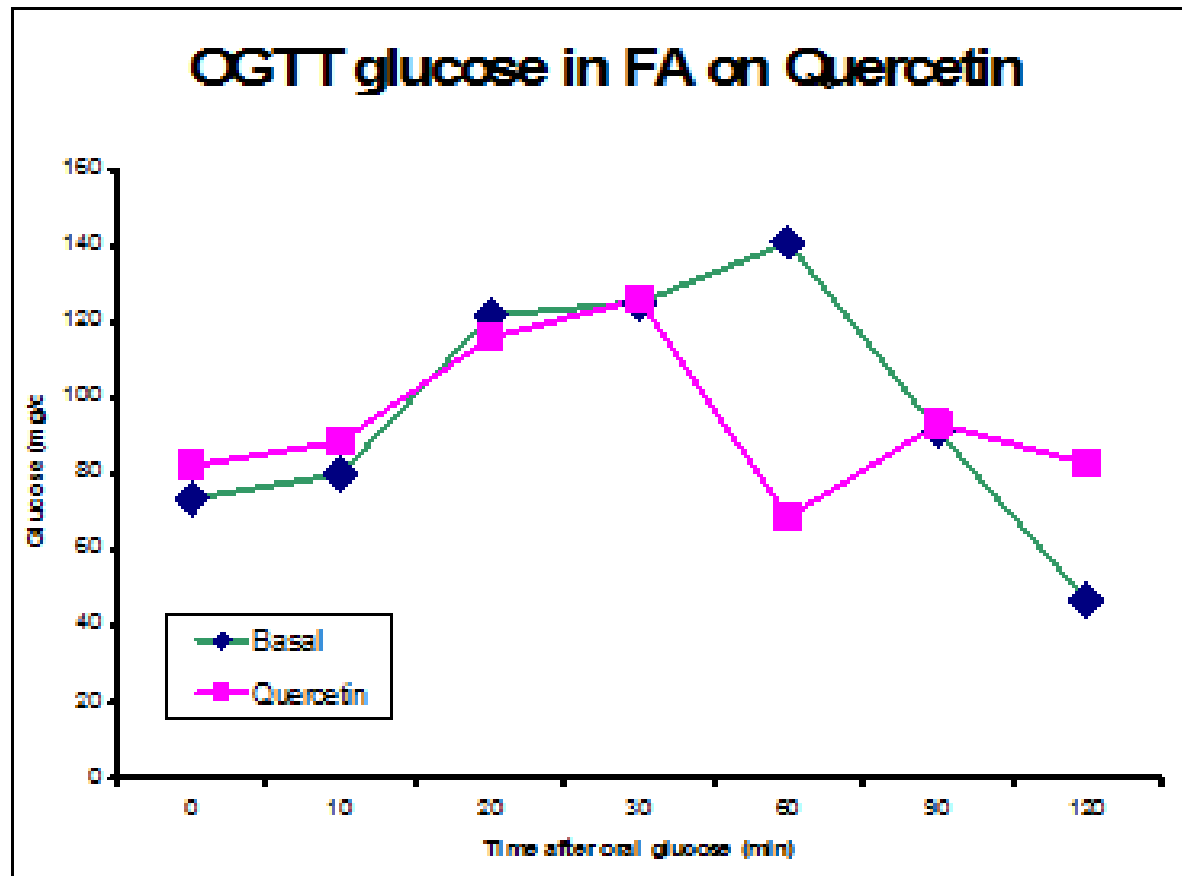
Monitoring for Quercetin effects

- We have measured levels of Quercetin in the blood to see if we can get optimal levels- it appears we can
- We are measuring ROS levels in blood and bone marrow to see if it is decreased after Quercetin- in the first few patients it appears that levels are reduced
- We also follow blood counts, growth and blood sugars closely to see the effects of the supplement

Progress on the study

- First three older (over 12 years old) patients enrolled and have completed treatment and blood level measurements (FDA requirement)- no one had severe side effects and the blood levels of the quercetin were what we wanted- similar levels that worked in the mouse studies
- We are seeing improvement in the colony count of baby blood cells.
- We are now enrolling younger children on the study- the first has nearly finished treatment

Preliminary results



AUC is better, the peak glucose is not as high, and there is no hypoglycemia at the end of the test

Conclusions

- Exposure to radiation is not necessary for transplant, and radiation-free transplant works well even for people with mismatched donors.
- Our new study is adjusting chemotherapy doses according to each patient's level of risk.
- We are testing a food supplement to prevent marrow failure, leukemia and and tumor growth in FA and preliminary results are encouraging.