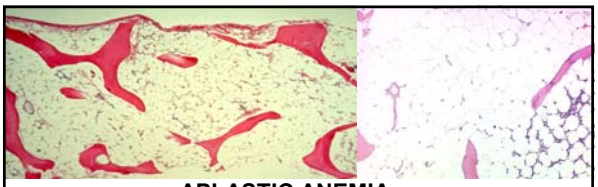
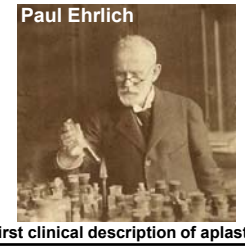


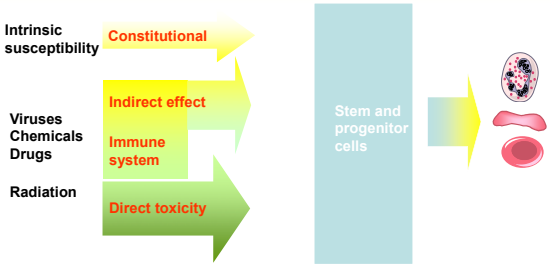
APLASTIC ANEMIA



- Identification of bone marrow as site of blood cell production
- Concept of the "hematopoietic stem cell"
- Development of bone marrow transplantation

First clinical description of aplastic anemia

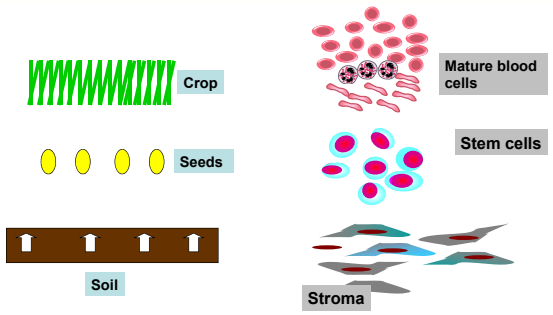
CAUSES OF APLASTIC ANEMIA



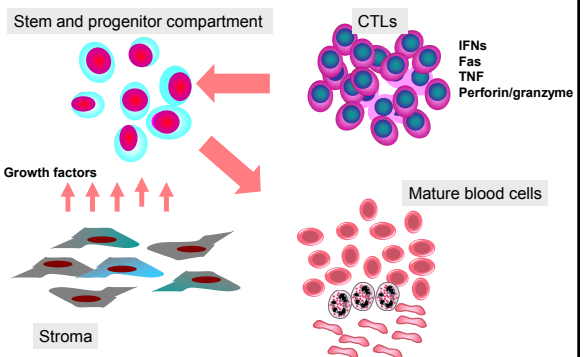
- Autoimmune attack
  - May be a common pathway
  - Likely most frequent cause of idiopathic aplastic anemia

Maciejewski & Young in Hoffman's Texbook of hematology 2008

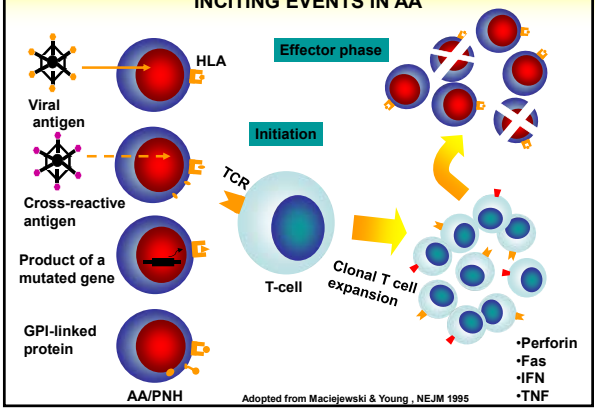
COMPONENTS OF BLOOD PRODUCTION



COMPONENETS OF THE PATHOPHYSIOLOGY OF IDIOPATHIC AA



INCITING EVENTS IN AA



RESULTS OF IMMUNOSUPPRESSIVE THERAPIES IN MAJOR CLINICAL TRIALS

STUDY	ATG	N	AGE (MEDIAN)	RESPONSE (%)	RELAPSE (%)	SURVIVAL
Bacigalupo et al., 2000[13]	hALG	100	16	77 (median of 96 days)	12 (3 yrs)	87 (at 5 yrs)
Kojima et al., 2000[14]	hALG	119	9	71 (6 mos)[a]	13 (4 yrs)[a]	83 (at 4 yrs)[a]
Frickhofen et al., 2003[15]	hATG	84	32	70 (4 mos)	38 (11 yrs)	58 (11 years)
Rosenfeld et al., 2003[16]		122	35	61 (6 mos)	35 (5 yrs)	55 (7 yrs)
Scheinberg et al., 2006[17]	hATG	104	30	64 (6 mos)[b]	37 (4 yrs)	80 (4 yrs)
Zheng et al., 2006[18]	hATG	142	34	78.7 (6 mos)[c]	-	81 (5 yrs)
Teramura et al., 200719;d	hATG	101	54	76 (1 yr)	42 (4 yrs)	88 (4 yrs)
Scheinberg et al., 2009[20]	hATG	77	26	62 (6 mos)[e]	26 (3 yrs)	90 (3 yrs)
Tichelli et al, 2010[21]	hATG	192	46	70[f] (median ff up 41 mos)	33 (6 yrs)	76 (6 yrs)
Atta et al., 2010[22]	hATG	71	19	59.5[g] (6 mos)	36	78.4 (2 yrs)
Afable et al., 2011[23]	hATG	67	49	58 (1 yr)[h]	16	64 ± 6 (5yrs)

SAA

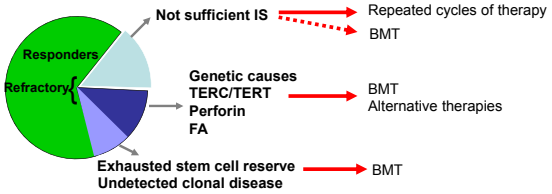
- hATG with CsA wait for 3 months
- If no response repeated rATG/CsA
- Alternative treatments with Campath

How long to wait for response?
What to do if CsA is to toxic?
How long to treat?
When to think about BMT?

HOW IMMUNOSUPPRESSION IS ADMINISTRED FOR LESS THAN SEVERE AA

•No standard established if counts not severely depressed.
Wait and watch and treatd if counts get worse
•CsA alone
•Campath
•Other immunosupressive agents
•Androgenic steroids

THERAPEUTIC CONSIDERATIONS



•Insuffcient immunosuppression
•Exhaustion of stem cell reserves
•Misdiagnosis
•Hereditary bone marrow failure

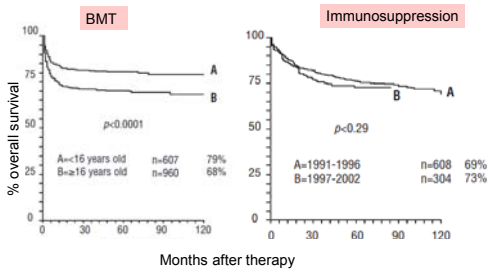
Immune pathogenesis

Non-immune pathogenesis

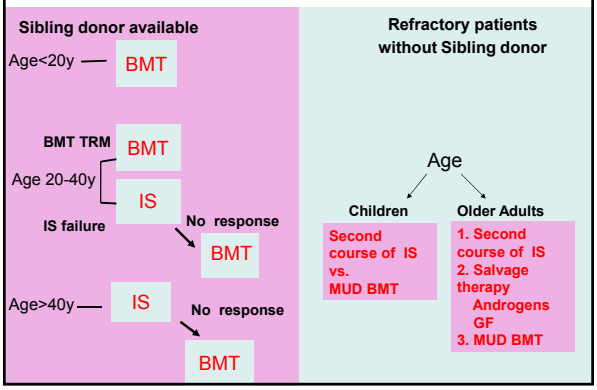
RESULTS OF ALLOGENIC BONE MARROW TRANSPLANTATION

N	Survival	Age	Source
133	59% at 16 y for TAI/Cy 95% at 4.4 y for ATG/Cy	55% <20y	France
211	89% at 20 y without GvHD 69% at 20 y with GvHD	18 y	FHCRC
915	Actuarial survival 77% for patients ≤16 y 68% for patients 17-40 y 54% for patients >40 y		EBMT
61	At 6 y 79%	14-40 y	Korea
71	94% at 8 y with CsA/MTx 78% at 7 y with CsA	20 y	GITMO
1699	5 y survival: 75% for patients ≤20 y 68% for patients 20-40 y 35% for patients >40 y		IBMTR

IMMUNOSUPPRESSION VS. BMT



TREATMENT ALGORITHM FOR sAA IN PATIENTS



CURRENT ISSUES

- Rabbit ATG vs horse ATG
- Horse ATG vs. Campath

- Newer agents to replace CsA

NEW DRUGS

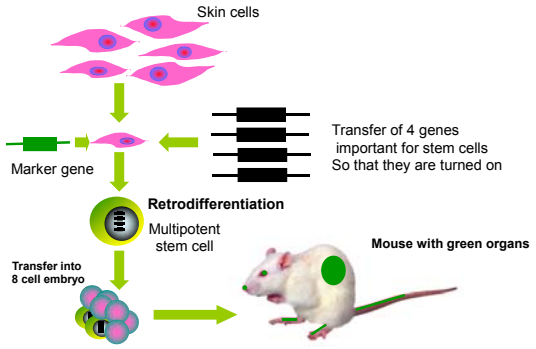
- Growth factors
  - Promacta (Elthormbopag)
  - Nplate (Thrombopoietin)
- New immunosuppressive agents
  - Arencia, Abatacept (soluble CTLA4)
  - Amevive, Alefacept (Soluble LFA-3)
  - Alemtuzamab (Campath)

ADULT STEM CELL RETRO-DIFFERENTIATION

- All cells in the body have a silenced potential to produce all tissues, this potential is encoded in the DNA which is identical in all cells.
- Multipotent stem cells have a potential to produce all tissues, similar to the ultimate stem cell: the fertilized egg.
- Through a process of differentiation, tissues and organs are formed and assume specific function and shape

Why it would not be possible to isolate cells and revert them in to a multipotent stem cell and direct their program to regenerate diseased tissues?

POTENTIAL OF THE ADULT STEM CELLS



THERAPEUTIC POTENTIAL OF THE ADULT STEM CELLS

Allogeneic bone marrow transplant is limited by the availability of the donor, toxicity of GvHD and inability to replace diseased bone marrow stem cells