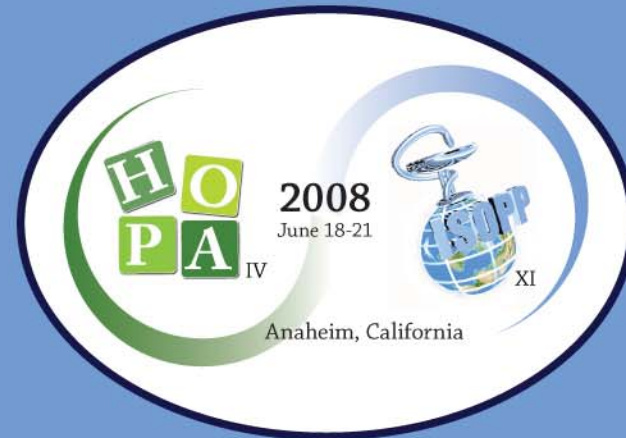


# Hematopoietic Cell Transplant

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# Disclosures/Conflict of Interest

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- Almost all of the medications discussed are off-label
- Jeannine S. McCune, PharmD received research funding from PDL Biopharma in June 2006

# Learning Objectives

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- To recognize the current role of HCT in the treatment of cancer patients
- To understand the ongoing research to expand the availability of HCT by improving the effectiveness of newer graft sources and reduced intensity conditioning
- To understand the recent advances in diagnosis and treatment of graft-versus-host disease (GVHD)
- To appreciate the role of personalized dosing of the HCT conditioning regimen and postgrafting immunosuppression

# Goal of HCT

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- Cure patient with no regimen-related toxicity and GVHD
  - Patients with nonmalignant condition cured through replacement of their hematopoiesis
  - Patients with cancer cured through conditioning regimen and/or graft versus tumor (GVT) effect

# HCT: Notable History

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- 1957: first bone marrow transplant (BMT) reported
- 1960s: development of preclinical models to improve clinical feasibility of BMT
- 1970s
  - Evaluation of autologous and allogeneic BMT in specific diseases
  - Calcineurin inhibitors to prevent GVHD
  - Recognition of GVT effect

# HCT: Notable History

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- 1980s
  - Expansion of BMT to other diseases
  - Successful transplant with grafts other than matched related donor (unrelated, haploidentical, umbilical cord blood)
- 1990s
  - Increasing use of peripheral blood progenitor cells (PBPC) as graft → term *hematopoietic cell transplant* (HCT) starts being used
  - Reduced intensity conditioning regimens introduced
  - Recognition that autologous HCT does not improve survival in breast cancer patients
- 2000s
  - Refinement of role of HCT in setting of newer agents
  - Worldwide annually ~ 20,000 allogeneic and 30,000 autologous HCT

# Factors Influencing Use of HCT

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- Type of HCT performed depends on
  - Recipient-specific factors
    - Type and status of disease
    - Age (<50 years for most patients)
    - Comorbidities (eg, liver or lung disease)
  - Donor-specific factors
    - Availability of a compatible donor

# Recipient-Specific Factors: Who Is Treated With an HCT?

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- Hematologic malignancies
  - Most common indications
    - Autologous HCT
      - Non-Hodgkin's lymphoma
      - Multiple myeloma
    - Allogeneic HCT
      - Acute leukemias
  - Additional indications
    - Chronic myeloid leukemia
    - Myelodysplastic syndrome
    - Hodgkin's lymphoma
- Solid tumors
  - Neuroblastoma
  - Renal cell carcinoma
- Nonmalignant diseases
  - Aplastic anemia
  - Paroxysmal nocturnal hemoglobinuria
  - Hemoglobinopathies
  - Congenital hematopoietic disorders

# Non-Hodgkin's Lymphoma

- Heterogeneous cancers of the lymphoid system, with histology affecting outcomes
- Below are examples of where HCT can be considered an option

	Autologous	Allogeneic
Follicular, $\geq 2$ nd line therapy	X	X
Mantle cell, consolidation	X	
Diffuse large B-cell		
Intermed high-high, 1st or 2nd line	X	
Chemosensitive, 1st relapse	X	
Lymphoblastic, $\geq 1$ st relapse		X

Adapted from Hahn T, et al. *Biol Blood Marrow Transplant*. 2001;7:308-31; NCCN Guidelines.  
Available at: [http://www.nccn.org/professionals/physician\\_gls/PDF/nhl.pdf](http://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf). Accessed 5/20/2008.

# Multiple Myeloma

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- HCT considered after induction therapy in patients with symptomatic (active) myeloma
- Disease response to autologous PBPCCT influences if patient undergoes future allogeneic HCT (eg, tandem)
  - Recent data suggest that autograft followed by nonmyeloablative allograft improves survival compared to tandem myeloablative autograft

# Acute Myeloid Leukemia in Adults

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- Induction: Allograft option for those who fail induction or had antecedent hematologic disease
- Post-remission therapy
  - For <60 yr old, cytogenetics affects role of allograft relative to chemotherapy
    - High risk: Allograft > chemotherapy
  - For ≥60 yr old: consider clinical trial with reduced intensity conditioning
- Second complete remission (CR): allograft > autograft

# Acute Myeloid Leukemia in Children

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- In first CR (except acute promyelocytic)
  - Allograft > chemotherapy in terms of disease-free and overall survival
    - Matched related bone marrow
  - Autograft and chemotherapy similar outcomes
- In second CR (all types of AML)
  - Little data comparing MRD allograft to chemotherapy
  - ASBMT panel consensus recommended use of MRD; alternative allografts on clinical trials

MRD = matched related donor.

Adapted from Oliansky DM, et al. *Biol Blood Marrow Transplant*. 2007;13:1-25.

# Acute Lymphoblastic Leukemia (ALL) in Children

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- In first CR in very high-risk Philadelphia chromosome positive: allograft > chemotherapy
- In second or greater CR: allograft appears equal to chemotherapy (but further study needed)
- Total body irradiation (TBI)-containing conditioning are recommended

# Role of Allogeneic HCT in Radiological and Nuclear Events

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- Response to a radiation disaster (ie, accidental or intentional) would need a “surge capacity” in hematologists/oncologists
  - Myelosuppression is frequent complication of radiation exposure
- National Marrow Donor Program (NMDP) and American Society for Blood and Marrow Transplantation established Radiation Injury Treatment Network (RITN, [www.ritn.net](http://www.ritn.net))
  - Voluntary consortium of HCT centers, donor centers, and umbilical cord blood banks
  - Develop treatment guidelines, educate health care professionals, coordinate situation response, and provide comprehensive evaluation and care for radiation injury victims

# Role of Allogeneic HCT in Radiological and Nuclear Events

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- Victims would need to be classified based on estimate of radiation dose
  - Not requiring medical intervention
  - Could benefit from supportive care (eg, filgrastim) to assist autologous marrow recovery
  - Require evaluation for HCT to treat marrow aplasia
  - Cannot be saved
- Role of allogeneic HCT as a life-sustaining measure is unclear
  - Patients will commonly have multiorgan damage
  - Experience in 31 patients after accidental radiation had disappointing median survival (1 month), high GVHD mortality rate (20%), and all 1-year survivors (4) had autologous recovery

# Recipient-Specific Factors: Age and Comorbidities

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- Ability to survive myeloablative conditioning traditionally restricted the number of cancer patients who could receive HCT
  - Most cancer patients are elderly, limiting use of potentially curative treatment
  - Impetus for developing reduced intensity conditioning (RIC) regimens
- Now that RIC regimens are developed, need a method for appropriately stratifying HCT recipients to determine best conditioning regimen

# Comorbidity

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- Definition: any distinct additional clinical entity that has existed or may occur during the clinical course of a patient with a primary (index) disease
- Charlson comorbidity index (CCI)
  - Some comorbidities (eg, hepatic and pulmonary) rarely encountered in HCT recipients due to existing exclusion criteria
  - Did not capture some frequent comorbidities, such as recent infections and psychiatric disturbances
  - Led to development of HCT-specific comorbidity index (HCT-CI)

# HCT-Specific Comorbidity Index (HCT-CI)

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- Developed and validated in myeloablative and nonmyeloablative HCT population (total N = 1055)
- Cumulative score
  - HCT-CI = 1: Arrhythmia, cardiac disease, inflammatory bowel disease, diabetes, cerebrovascular disease, psychiatric disturbance, mild hepatic, obesity, infection
  - HCT-CI = 2: Rheumatologic, peptic ulcer, moderate/severe renal, moderate pulmonary
  - HCT-CI = 3: Prior solid tumor, heart valve disease, severe pulmonary, moderate/severe hepatic
- Predicted nonrelapse mortality and survival

# HCT-Specific Comorbidity Index (HCT-CI)

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- Being used in retrospective evaluations to compare outcomes
  - Between myeloablative vs RIC conditioning (to allow for optimal design of future phase 3 trials)
  - Between institutions
- HCT-CI predicts toxicity, nonrelapse mortality, and overall survival better than Karnofsky performance status (KPS)
  - Weakly correlates ( $R^2 < 0.2$ ) with KPS
  - Both should be assessed before HCT to stratify patients

# Donor-Specific Factors

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- Gender
- Underlying comorbidities of donor
- Degree of match between donor and recipient for human leukocyte antigen (HLA)
  - A, B, C, DR, DQ
  - Definition of matched donor evolves as the technology evolves to more precisely conduct HLA typing
    - Resolution: Low (antigen) to intermediate (identify a couple potential alleles) to high (identify specific allele)
    - If matched at low resolution, may be mismatched at high resolution
    - Increasing number of HLA mismatches associated with increased risk of graft failure, GVHD, and mortality

# Summary:

## Factors Influencing Use of HCT

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- Hematologic diseases are most common indications for HCT
- The development of RIC regimens and improved HLA typing (with the subsequent ability to increase the number of unrelated, haploidentical and umbilical cord grafts) has expanded the availability of allogeneic HCT
- Stratification of comorbidities by HCT-CI and KPS valuable for future studies to determine which patient populations would benefit from only RIC regimens or who should be studied in phase 3 trials of myeloablative vs RIC conditioning

# Expanding the Availability of HCT: Donor Grafts

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- Matched sibling donor possible for a few (~25%)
- Unrelated donor
  - Match found for 10% (poorly represented ethnicities) to 60% Caucasians
  - Considerable time needed for suitably HLA-matched unrelated donor (MUD)
  - Cannot identify suitable MUD for ~15,000 patients annually → need grafts with immediate availability (ie, haploidentical and umbilical cord blood)

# Haploidentical Donors

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- Virtually all have one haplotype-mismatched donor
  - Can select from best of any relatives based on age, infectious disease status, and natural killer (NK) reactivity
  - Immediate access to donor-derived cellular therapies
- In 1980s, mortality risk was too high
- Recent interest due to improved patient selection (by disease and genetics), supportive care, and GVHD prophylaxis

# Umbilical Cord Blood

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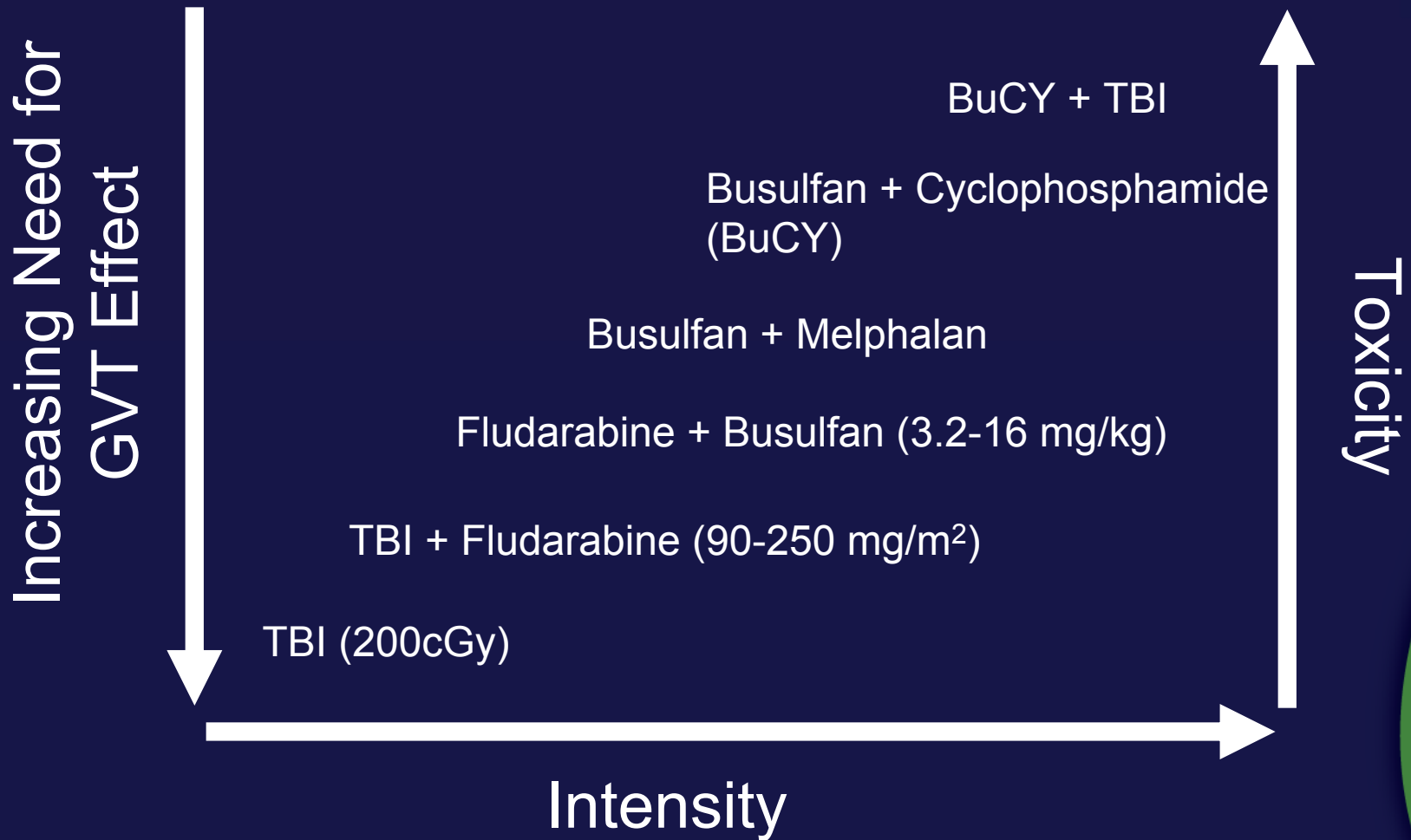
- Use in adults limited by small cell dose, resulting in delayed engraftment
- Double cord blood leads to rapid neutrophil recovery with one single cord ultimately “winning”
  - Have increased incidence of acute GVHD, long-term thrombocytopenia in subset of patients
- Many unanswered questions about HLA matching, RIC, minimum cell dose, immune reconstitution, ex vivo expansion

# Expanding the Availability of HCT: Conditioning Regimens

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- Purpose: immunosuppress recipient, eradicate malignancy, create marrow “space”
- Types
  - Myeloablative
  - RIC, which includes nonmyeloablative
    - Rely more on the graft versus tumor effect

# Increasing Variability in Conditioning Regimens



TBI = total body irradiation.

Deeg HJ, et al. *Leukemia*. 2006;20:1701-5.

# Myeloablative Conditioning

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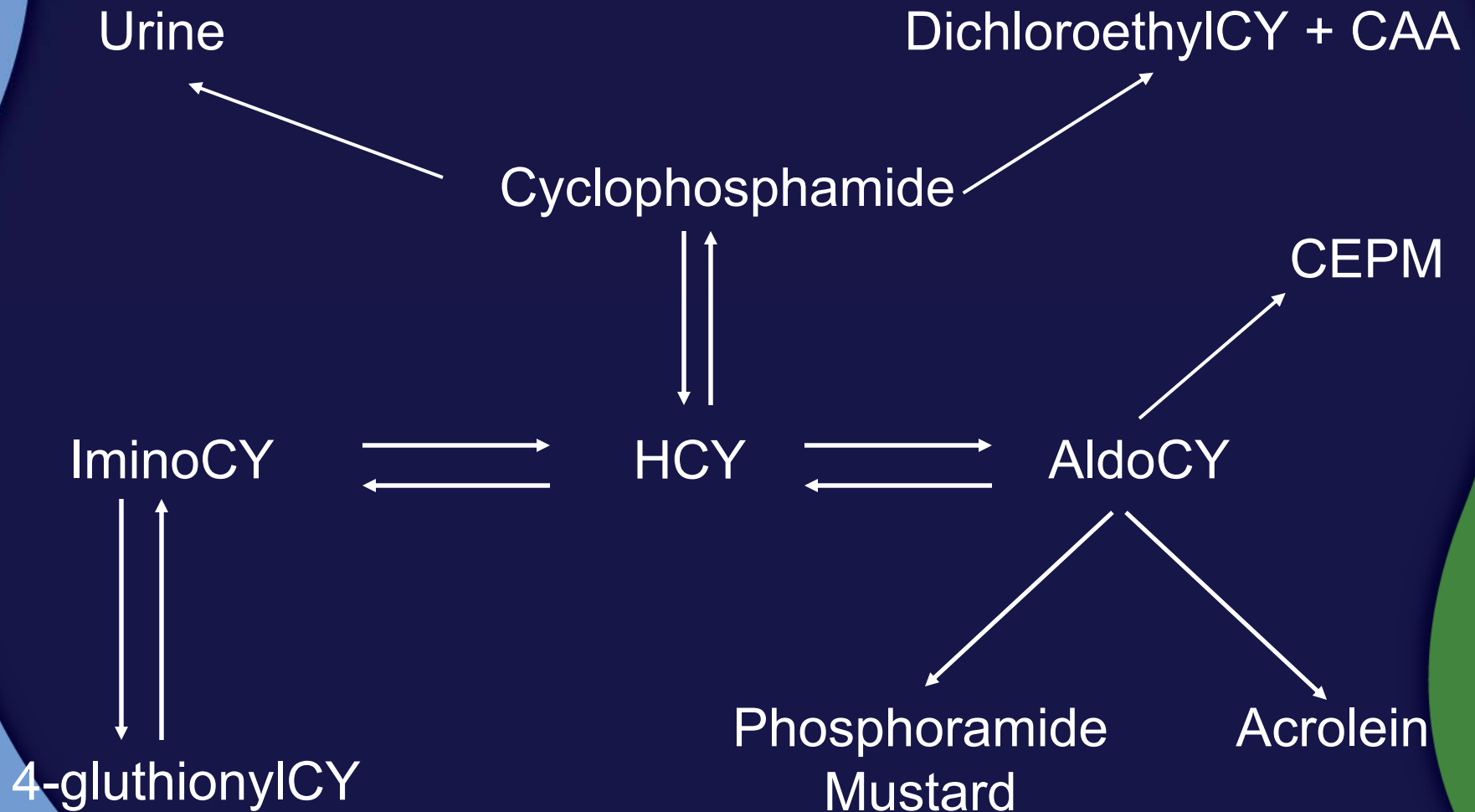
## ■ Examples

- Cyclophosphamide/total body irradiation (CY/TBI)
- Busulfan/cyclophosphamide (Bu/CY)
- Busulfan/fludarabine
- Busulfan, melphalan, thiotepa

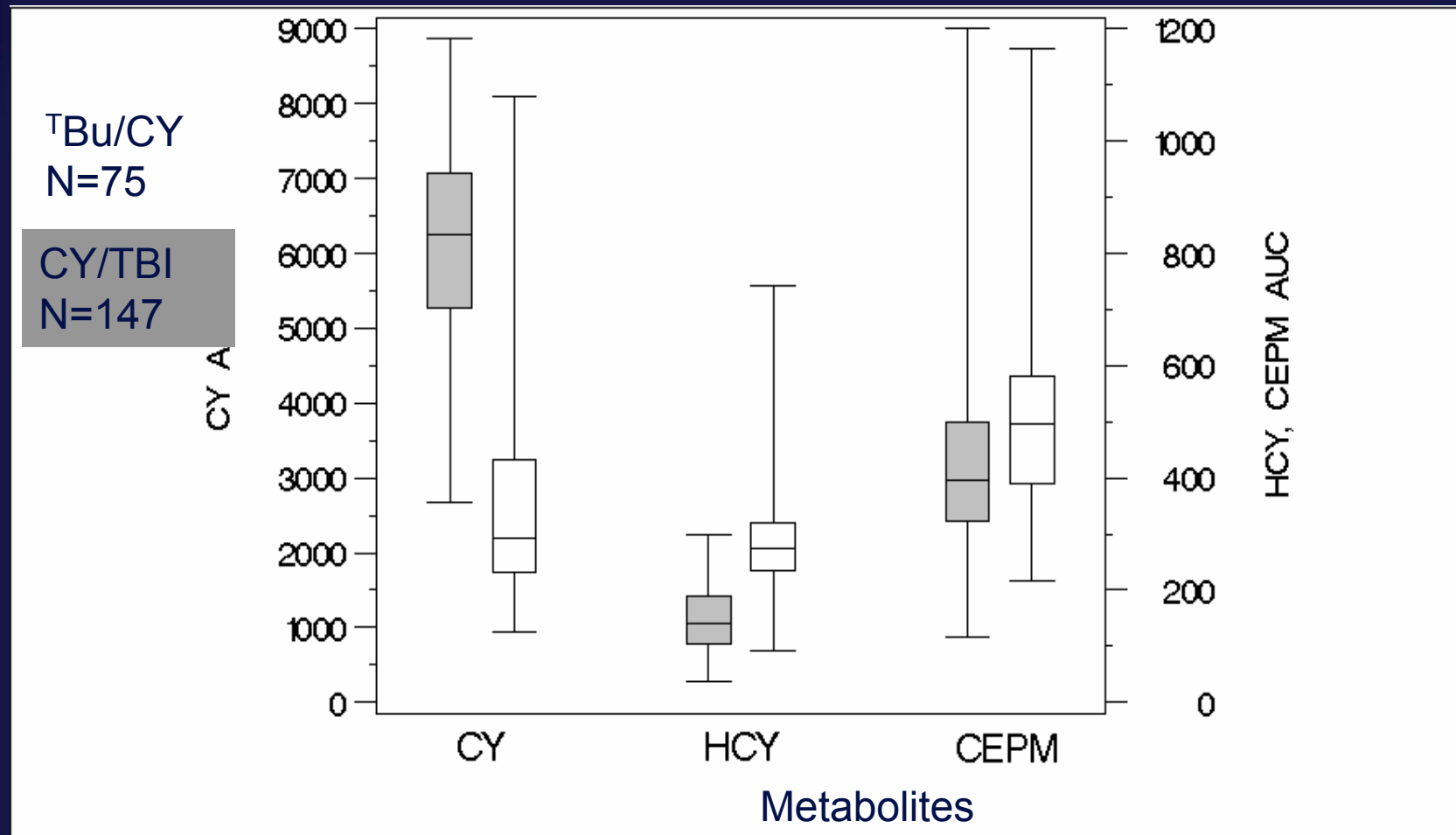
## ■ Nonhematologic toxicity dose limiting, with considerable interpatient variability in response and toxicity

- Efforts focused upon lowering toxicity by more targeted delivery of radiation (monoclonal antibodies) or personalized drug dosing

# Cyclophosphamide



# CY Pharmacokinetics Depend on Conditioning-Regimen



# Can Personalized Dosing Improve CY/TBI?

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- High AUC of carboxyethylphosphoramidate mustard (CEPM) was associated with higher risk of liver toxicity
  - But it was expected that hydroxycyclophosphamide (HCY) AUC would be related to liver toxicity because HCY toxic to murine sinus endothelial cells (SEC)
- It is feasible to target CY doses based on the AUC of CEPM and AUC of HCY
  - Lower CEPM AUC to lower risk of hepatotoxicity
  - Maintain AUC of HCY to lowest AUC in prior study to maintain engraftment
  - Rapid population pharmacokinetic modeling needed in future studies to more accurately personalize CY dose to achieve metabolite AUCs
- Evaluating if personalization of CY doses based on metabolite AUCs decreases nonrelapse mortality

# CY Pharmacodynamics Differ With Conditioning Regimens

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- With TBU/CY, there were no statistically significant associations between the AUC of CY or its metabolites and liver toxicity, non-relapse mortality, relapse, or survival (all  $P > .15$ )
  - Oral busulfan doses targeted to  $C_{ss}$  800-900 ng/mL
  - Personalization of CY doses based on its pharmacokinetics in TBU/CY unlikely to be beneficial
- CY, like busulfan, pharmacodynamics differ between conditioning regimens
- Lower toxicity by using bu/fludarabine regimen?

# Busulfan

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- Available IV and PO formulations
- Busulfan pharmacodynamics differ based on underlying disease, age of recipient, conditioning regimen
- Many centers use IV busulfan with the “perception” of less liver toxicity, less pharmacokinetic variability, and less need for personalization of busulfan doses based on pharmacokinetic variability

# Busulfan Pharmacokinetics: Comparison of IV to PO

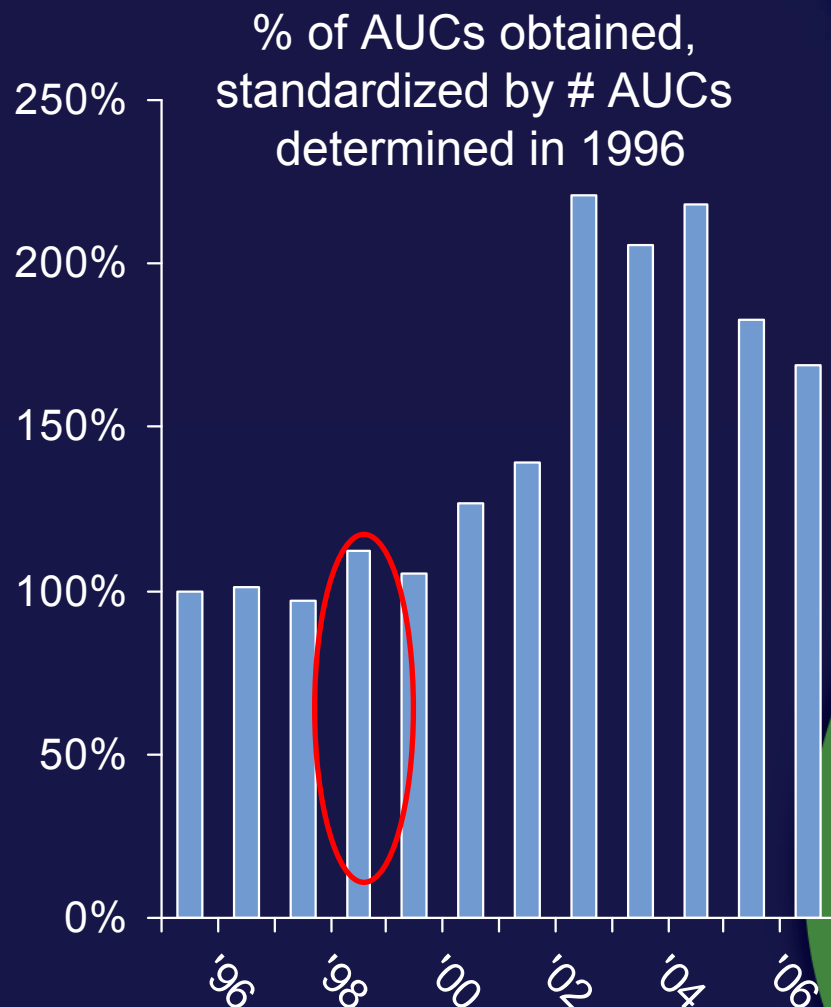
Busulfan Clearance (mL/min/m <sup>2</sup> )		
Day	IV	PO
N	57	1040
1	107 ± 27 25%	108 ± 23 21%
2	102 ± 22 22%	107 ± 24 22%
3	99 ± 23 23%	110 ± 25 23%

Day 1 Dose (mg/kg)	1 PO Q6hr	3.2 IV Q24hr	4 IV Q24hr
N	21	21	15
% in target C <sub>ss</sub> range of 800-1000 ng/mL:			
Day 1	62%	19%	60%
Day 1-4	81%	86%	93%
Average (range) C <sub>ss</sub>	906 (730- 1074)	842 (714- 966)	939 (819- 1038)

- Are the lower rates of liver toxicity with IV busulfan due to lower busulfan AUC with 0.8 mg/kg IV busulfan vs 1 mg/kg PO busulfan?

# Personalization of Busulfan Doses Is Needed with IV Busulfan

- Pharmacodynamic relationships with Bu/CY exist, regardless of administration route
- Increasing use of personalization of busulfan doses by pharmacokinetics since IV busulfan was FDA approved (2/99)
- High busulfan exposure related to lower overall and progression-free survival in bu/fludarabine conditioned patients
  - Fludarabine AUC not predictive

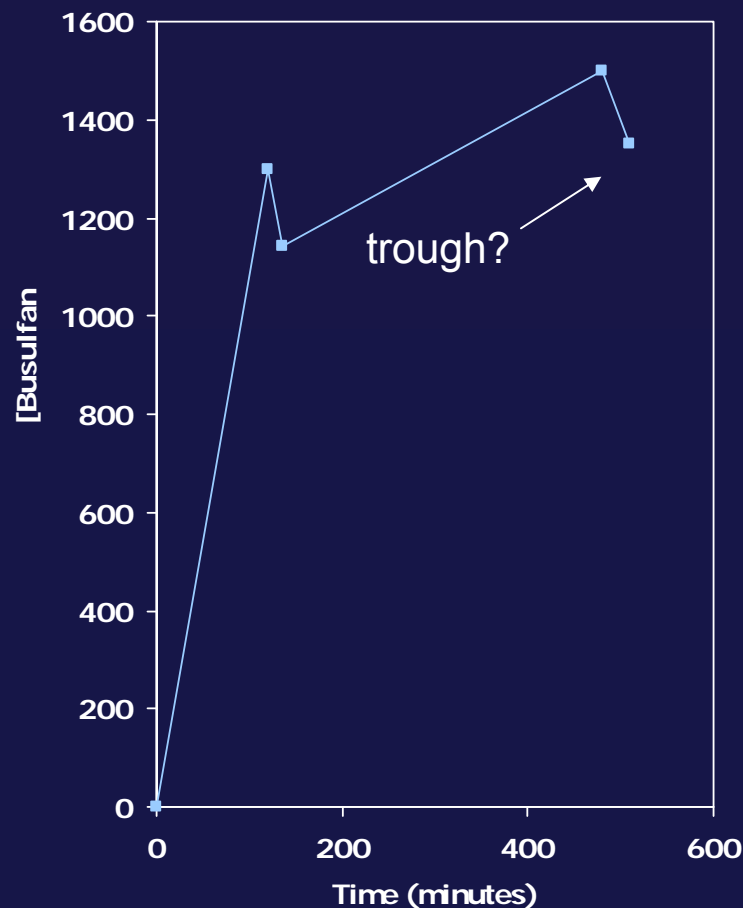


Geddes M, et al. *Biol Blood Marrow Transplant.* 2008;14:220-8.

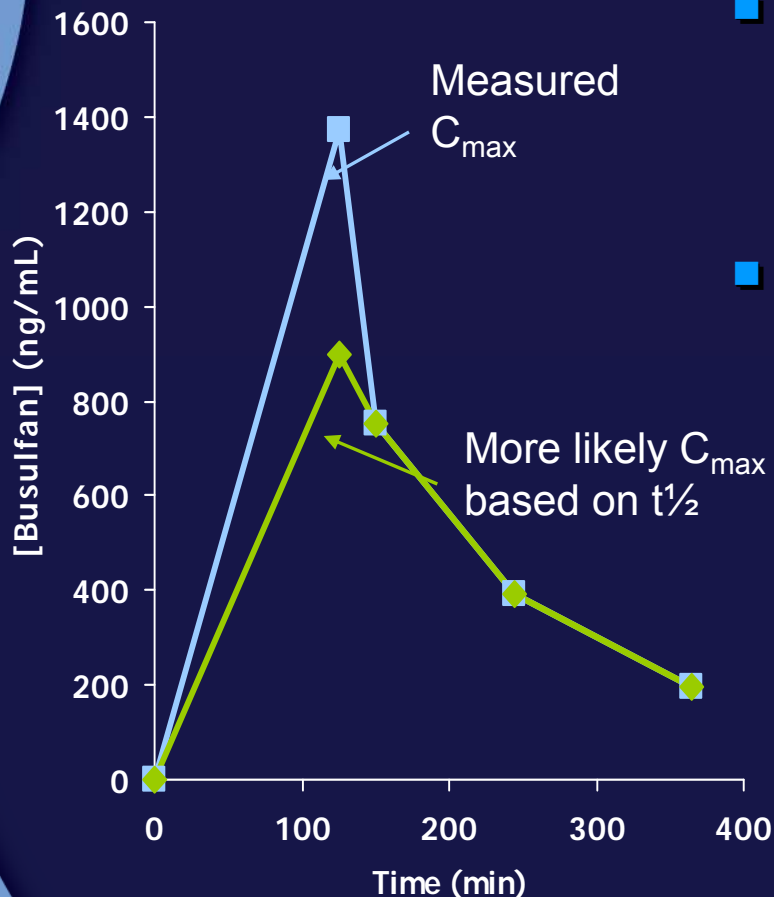
Bornhauser M, et al. *Blood.* 2003;102:820-6.

# Careful Attention Needed for Busulfan Pharmacokinetic Sampling

- Ensure the exact time of blood draw, using the same clock, is written
- Ensure troughs are drawn prior to starting infusion of next dose



# Careful Attention Needed for Busulfan Pharmacokinetic Sampling



- At end of infusion, make sure administration and flush is completed. If not, concentrations may be high

- Example:

Time (min)	Conc (ng/mL)
125	1372
150	750
245	391
365	198

1 half-life = 25 min?

2 half-lives = 215 min

# Reduced Intensity Conditioning

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- Increase the availability of allogeneic HCT to older patients or those with comorbidities
- Use lower doses of conditioning regimen, and rely on allografts to provide GVT effect
  - Multitude of RIC regimens with no clear advantage of one. Many utilize fludarabine and calcineurin inhibitor and mycophenolate mofetil
  - Nonmyeloablative fludarabine/TBI most commonly used in those receiving unrelated donor grafts

# Criteria for RIC

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- No eradication of recipient hematopoiesis
- Prompt hematologic recovery (<4 weeks) if graft rejection (but also no GVT)
- Presence of mixed chimerism upon engraftment
  - Established even across HLA antigen barriers
  - Period of time in which the recipient and donor cells are circulating concurrently in the recipient's blood

# Longitudinal Chimerism Analysis

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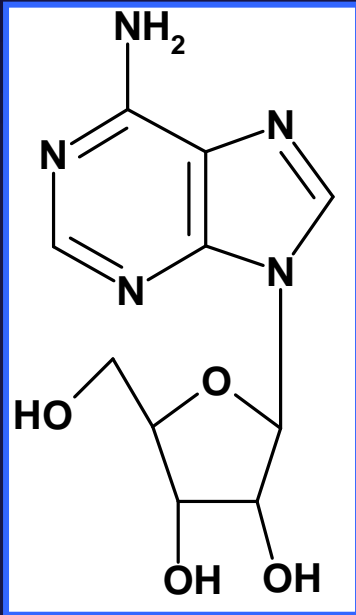
- Evaluate chimerism in different cell types
- Temporal pattern of chimerism depends on conditioning regimen
- Recent data suggest % donor chimerism predictive of relapse, acute GVHD, survival in fludarabine/TBI conditioned patients
  - Too low (ie, <40%-50%) donor chimerism early, increase risk of rejection and relapse
  - Too high % (ie, >90%) donor chimerism early, increased risk of acute GVHD (which has no GVT)

# Delicate Balance of Recipient and Donor With RIC

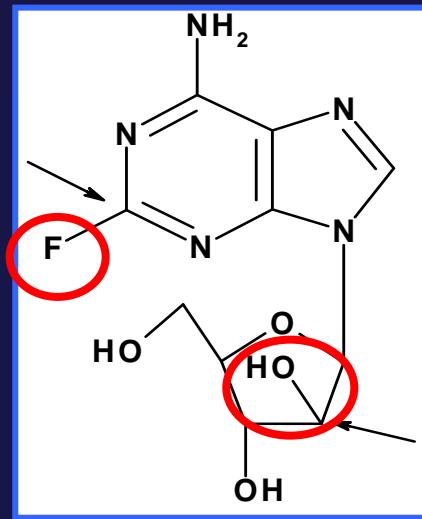
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- GVHD and GVT continue to be tightly linked
- Need some GVT (which usually comes with some GVHD) but not so much GVHD, which is most common cause of nonrelapse mortality in RIC-conditioned patients
- Present understanding is that the donor T cells react with host cells of the HLA-matched but genetically nonidentical recipient, specifically targeting the nonhematopoietic tissue (ie, GVHD) along with their hematologic malignancy (ie, GVT)
- Work ongoing to segregate these polymorphic differences such that donor T cells react with host leukemic cells without damaging the nonhematopoietic tissues or the engrafting donor hematopoietic progenitor cells

# Fludarabine and Fludarabine Monophosphate

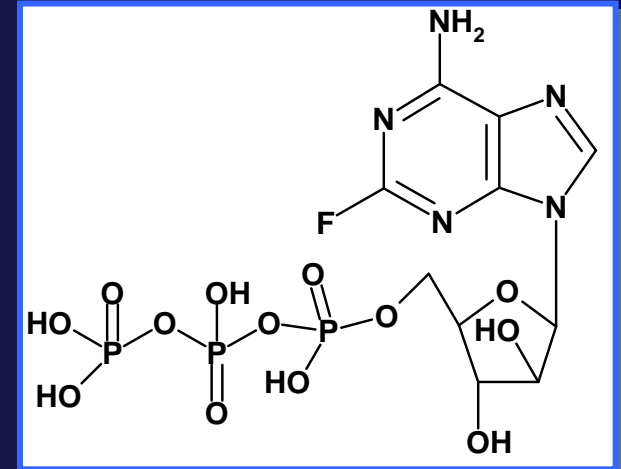


Adenosine



Fludarabine

2-Fluoroadenine-9-β-D-arabinofuranoside



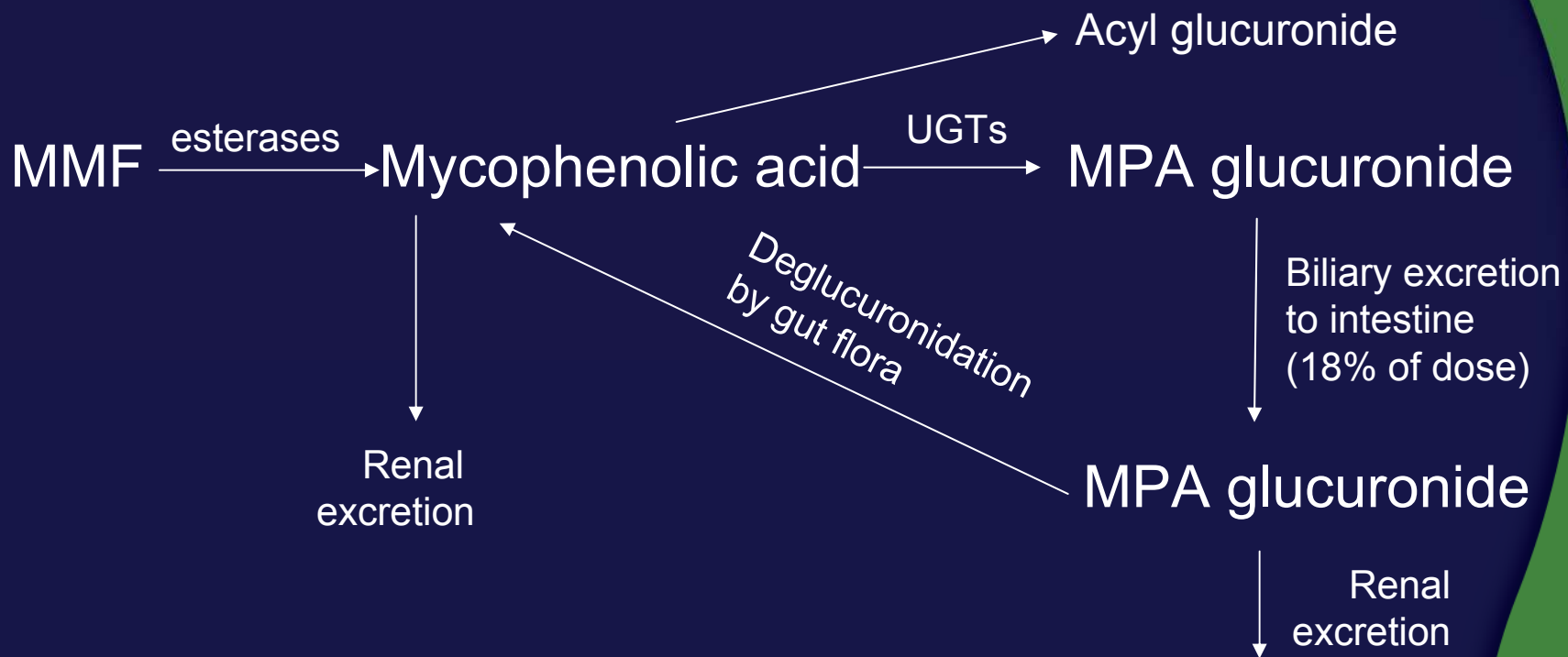
Fludarabine Triphosphate

# Mycophenolate Mofetil (MMF)

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- Prodrug which forms mycophenolic acid (MPA), which inhibits inosine monophosphate dehydrogenase (IMPDH), which is required for de novo purine synthesis in activated lymphocytes
- Nausea often problematic, data in solid organ transplant recipients suggest less nausea with enteric-coated MPA
- Pharmacodynamic correlations recognized for 10+ years in solid organ transplant patients
- Three trials comparing fixed dose (1 g BID) vs “concentration controlled (CC)” in renal transplant patients
  - No difference in graft loss in all 3 trials, one trial showed improved renal function in those receiving CC MMF with reduced calcineurin inhibitor doses
  - MMF toxicity data mixed, one trial shows more leukopenia/thrombocytopenia with CC MMF while no difference in another

# Mycophenolate Mofetil (MMF)



# Pharmacodynamics After MMF Use for GVHD Prophylaxis

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- Maris et al. *Blood*. 2003
  - Shorter dosing intervals may be needed in HCT recipients because of shorter half-life
  - Led to use of TID MMF in nonmyeloablative conditioned patients with unrelated donor graft (where rejections were more common)
- Osunkwo et al. *BBMT*. 2004
  - 34 children with various malignancies, preparative regimens (21 myeloablative), grafts (22 cords) and HLA disparity, tacrolimus/MMF
  - Grade II-IV acute GVHD occurred in all 6 children with total MPA trough  $<1$   $\mu\text{g}/\text{mL}$  and 1/6 with trough of 1-3.5  $\mu\text{g}/\text{mL}$

# Pharmacodynamics After MMF Use for GVHD Prophylaxis

- Jacobson et al. *Clin Pharmacol Ther.* 2005
  - 87 adults, RIC, various grafts, Cyclosporine (CSP)/MMF
  - Acute GVHD associated with free MPA AUC < 300 ng/mL\*hr (58% vs 35%, P = .05). No association with trough concentrations.
  - Higher cumulative incidence of engraftment associated with total MPA trough > 1 µg/mL (P < .01). All engraftment failures in cords.
- Giaccone et al. *Blood* 2005
  - 85 patients, hematologic malignancies, FLU/TBI, HLA-matched unrelated-donor, CSP/MMF post-grafting
  - 16 patients with a total MPA C<sub>ss</sub> <3 µg/mL had low (<50%) donor T-cell chimerism (P = .03); 6 patients with MPA C<sub>ss</sub> <2.5 µg/mL had graft rejection
  - Elevated unbound C<sub>ss</sub> was associated with CMV reactivation (20 vs 31 ng/mL, P = .03)
  - No significant associations with acute GVHD or relapse

# Summary: Expanding Availability of HCT and Personalized Dosing

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- The development of RIC regimens and improved HLA typing (with the subsequent ability to increase the number of unrelated, haploidentical and umbilical cord grafts) has expanded the availability of allogeneic HCT
- Personalized drug dosing is widely accepted for both IV and oral busulfan, but more data is needed regarding its potential benefit for patients receiving MMF or cyclophosphamide

# Graft-Versus-Host Disease

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- Boundary between acute and chronic GVHD was traditionally based on time, now based on clinical symptoms
- In 2006, for the first time, comprehensive diagnostic, staging, and response criteria for chronic GVHD (cGVHD) were established
  - Still “work in progress” and currently being validated retrospectively

# Acute GVHD Prophylaxis

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- Grade II–IV acute GVHD occurs in 20% to 50% of HLA-matched sibling grafts and 50% to 80% of HLA-mismatched sibling or HLA-identical unrelated donors
- Unfortunately, little change in GVHD prophylactic regimens for myeloablative regimens over past 20 years
- Nonmyeloablative HCT
  - Similar incidence and severity of acute GVHD as myeloablative HCT
  - GVHD rates not influenced by more frequent dosing or extending duration of MMF
  - Extended duration of cyclosporine (CSP) dosing does lower acute GVHD rates

# Acute GVHD Treatment

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- Despite many promising therapies, none have been positive in prospective randomized comparison
  - Monoclonal and polyclonal antilymphocyte antibodies, anti-TNF alpha antibodies, proinflammatory cytokine-modifying agents, extracorporeal photopheresis or infusion of mesenchymal stromal cells
- EXCEPT oral beclomethasone dipropionate (BDP) in patients with steroid refractory gastrointestinal GVHD had positive data in a prospective, randomized, placebo-controlled group
  - No data on absorption or "nonabsorption" of BDP
  - BDP decreased risk of GVHD treatment failure and improved survival
    - Effects were even more pronounced in recipients of mismatched or unrelated transplants
  - Reduction in mortality was primarily due to a reduction in deaths from infections and deaths from relapse, not in deaths from GVHD
  - Confirmatory trial needed
- Systemic corticosteroids still remain first-line treatment, with ~50% response rate

# Chronic GVHD

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- Minimal insight into its basic biology, no validated biomarkers
- Risk factors
  - Nonintensity of conditioning regimen
  - Nonmodifiable: older age of recipient, certain diagnoses (eg, CML), and lack of an HLA-matched donor
  - Modifiable: younger donor, avoiding a multiparous female donor, umbilical cord blood or bone marrow graft rather than PBPC, and limiting the CD34+ and T-cell dose infused
- Development of acute GVHD is a major predictor for chronic GVHD and 70% – 80% of those with grade II to IV acute GVHD develop chronic GVHD
- Ongoing research:
  - Phase 2 studies suggest benefit from extracorporeal photopheresis (ECP) and rituximab
  - MMF and enteric-coated MPA as an adjunct to standard front-line cGVHD therapy

# Examples of NIH Consensus Guidelines: Diagnosis

Affected Organ	Diagnosis	Distinctive	Other Features	Seen with Acute & Chronic GVHD
Eyes		New onset dry, gritty, or painful eyes	Photophobia; Periorbital hyperpigmentation; Erythema of the eyelids with edema	
GI tract	Esophageal web  Stricture or stenosis in upper to mid third of esophagus		Pancreatic insufficiency	Anorexia; nausea; vomiting; diarrhea; weight loss; failure to thrive (peds)

# Summary: GVHD

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- Acute GVHD
  - Prophylaxis has minimally changed for myeloablative conditioning, while incremental improvements are occurring with RIC
  - Treatment largely unchanged
- The NIH consensus guidelines will impact the diagnosis of chronic GVHD with the end goal of identifying methods for its prevention and treatment

# Overall Summary

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- HCT mainly used for treatment of hematologic malignancies
- Use of HCT is expanding due to increasing availability of novel graft sources and the refinement of RIC
- Personalization of chemotherapy and immunosuppressant dosing continues to be a unique opportunity for pharmacists to improve the outcomes for HCT recipients
- Continued research is needed to improve outcomes for HCT recipients who experience acute and/or chronic GVHD