SOS in Hepatology

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SOS in Hepatology

1. Pyrrolizidine alkaloids intoxication (PA)
2. Hematopoietic stem cell transplantation (HSCT)
3. Chemotherapy for colorectal cancer (CRC)
4. Other contexts

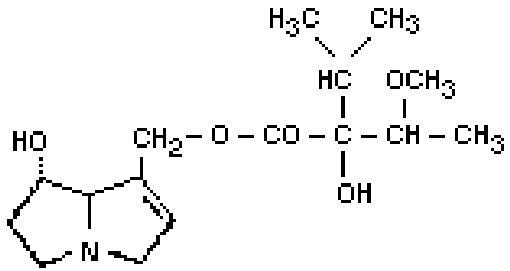
PA-Related Liver Disease

- A disease in humans and cattle (1920 - 1950s)
- Abdominal pain, ascites, portal hypertension, liver dysfunction
- Acute, subacute and chronic variants
- Recovery 50%. Rapid demise 20%. Decompensated chronic liver disease 30%

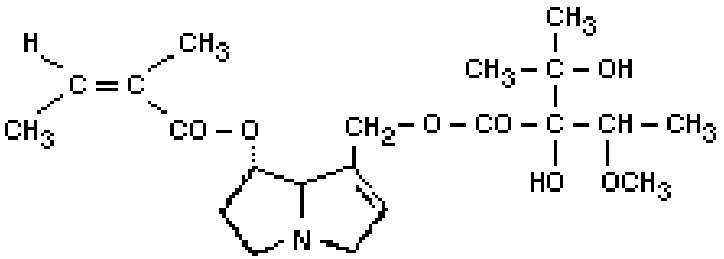
A distinct clinical syndrome

Pyrrolizidine alkaloids

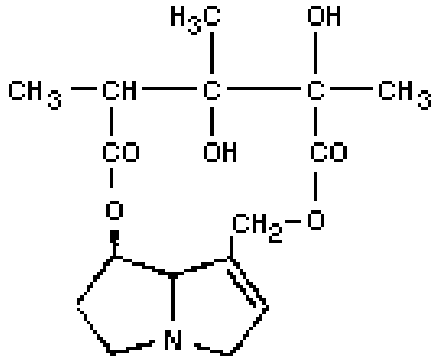
Heliotropine $C_{16}H_{27}NO_5$
CAS Registry No. 303-33-3



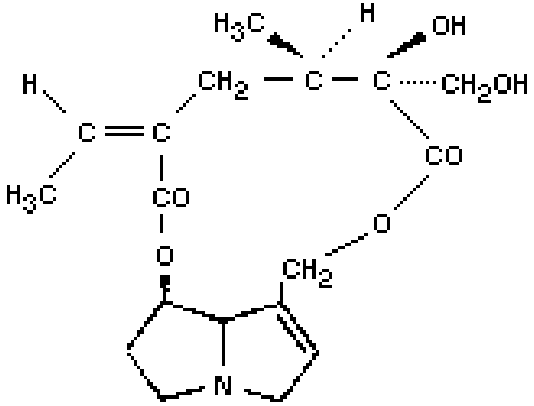
Lasiocarpine $C_{21}H_{33}NO_7$
CAS Registry No. 303-34-4



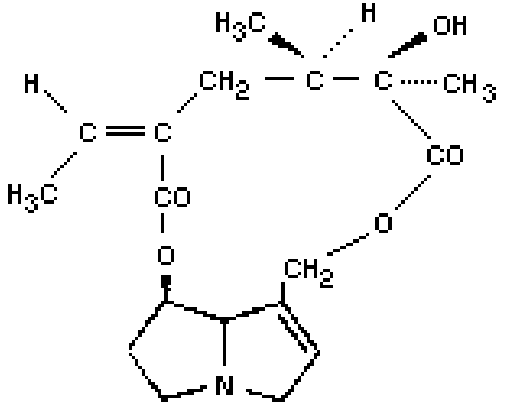
Monocrotaline $C_{16}H_{23}NO_6$
CAS Registry No. 315-22-0



Retrorsine $C_{18}H_{25}NO_3$
CAS Registry No. 480-54-6



Senecionine $C_{18}H_{25}NO_5$
CAS Registry No. 130-01-8



PYRROLIZIDINE ALKALOIDS

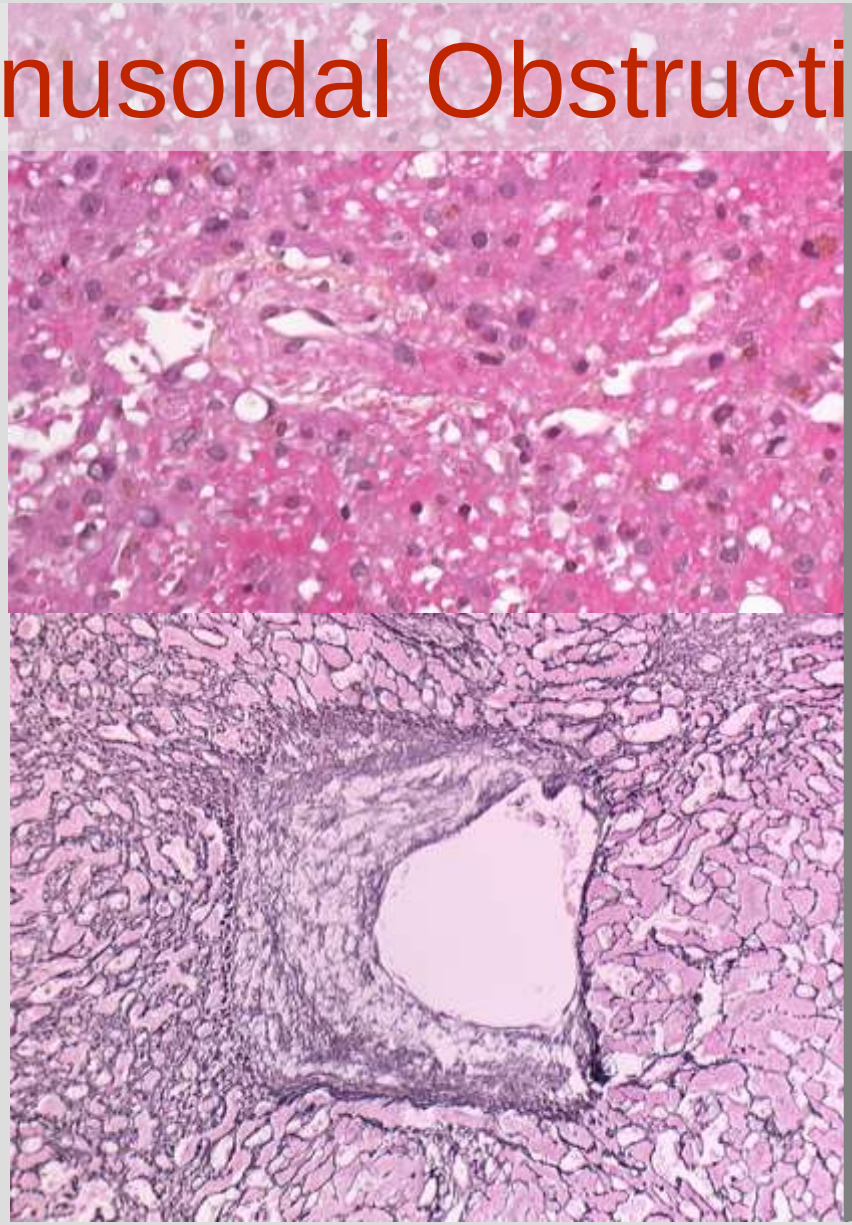
Herbal medicine	Bush tea	Contaminated wheat
Sporadic	Endemic	Epidemic

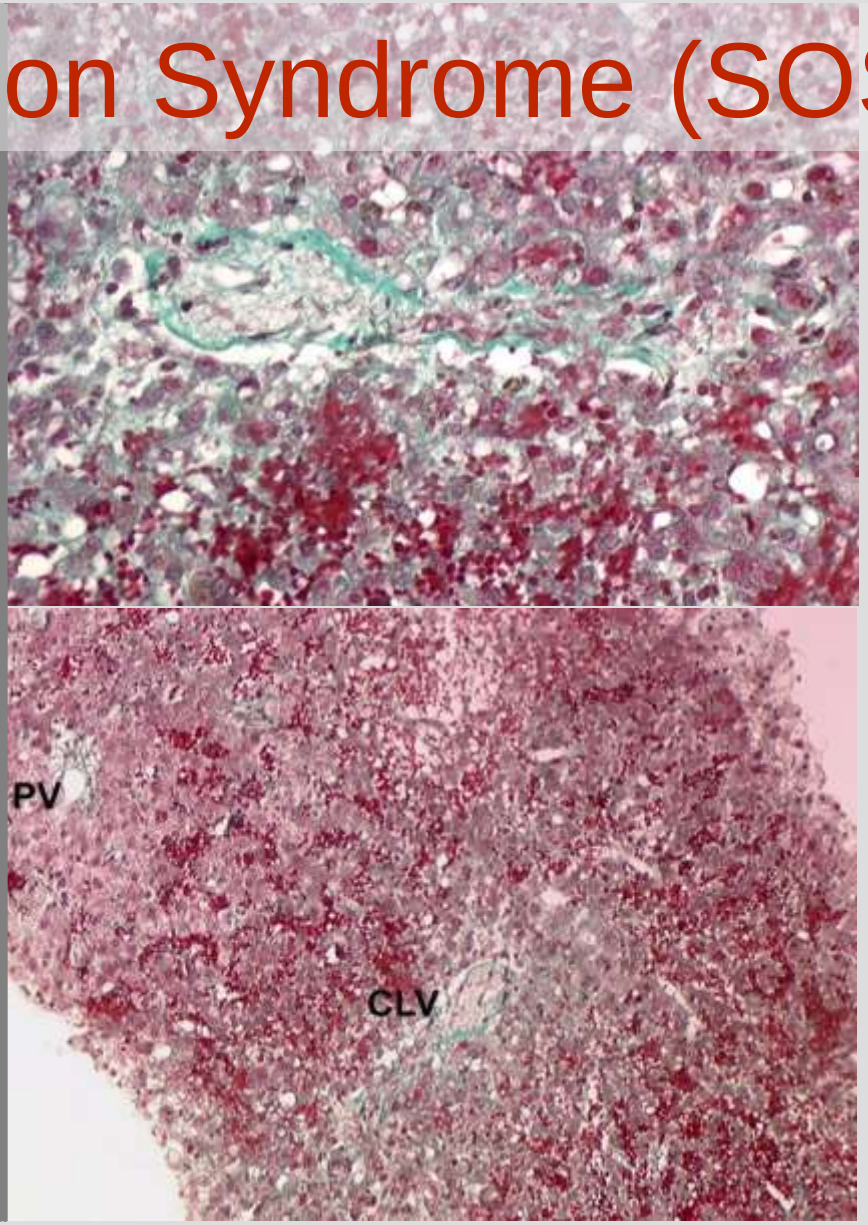
Pyrrolizidine Alkaloids : From VOD to SOS

- 1920 Extensive fibrosis/cirrhosis venocentric
- 1950 Central hemorrhagic necrosis,
  Non-thrombotic occlusion of central vein
- 1970 ‘Devastation of endothelium’
  RBC in the space of Disse
  Massive dropout of liver cells
- 1999 The monocrotaline rat model

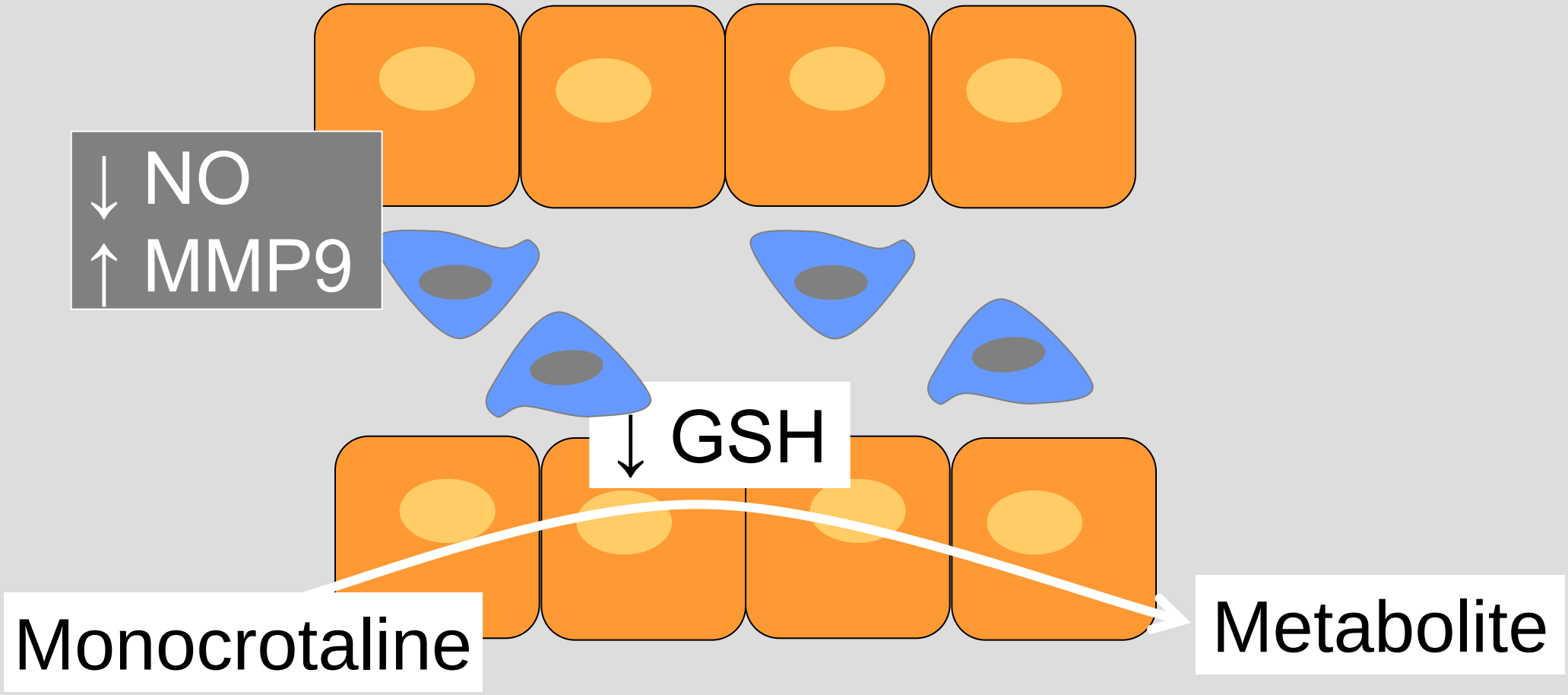
Veno-Occlusive Disease (VOD)

Sinusoidal Obstruction Syndrome (SOS)





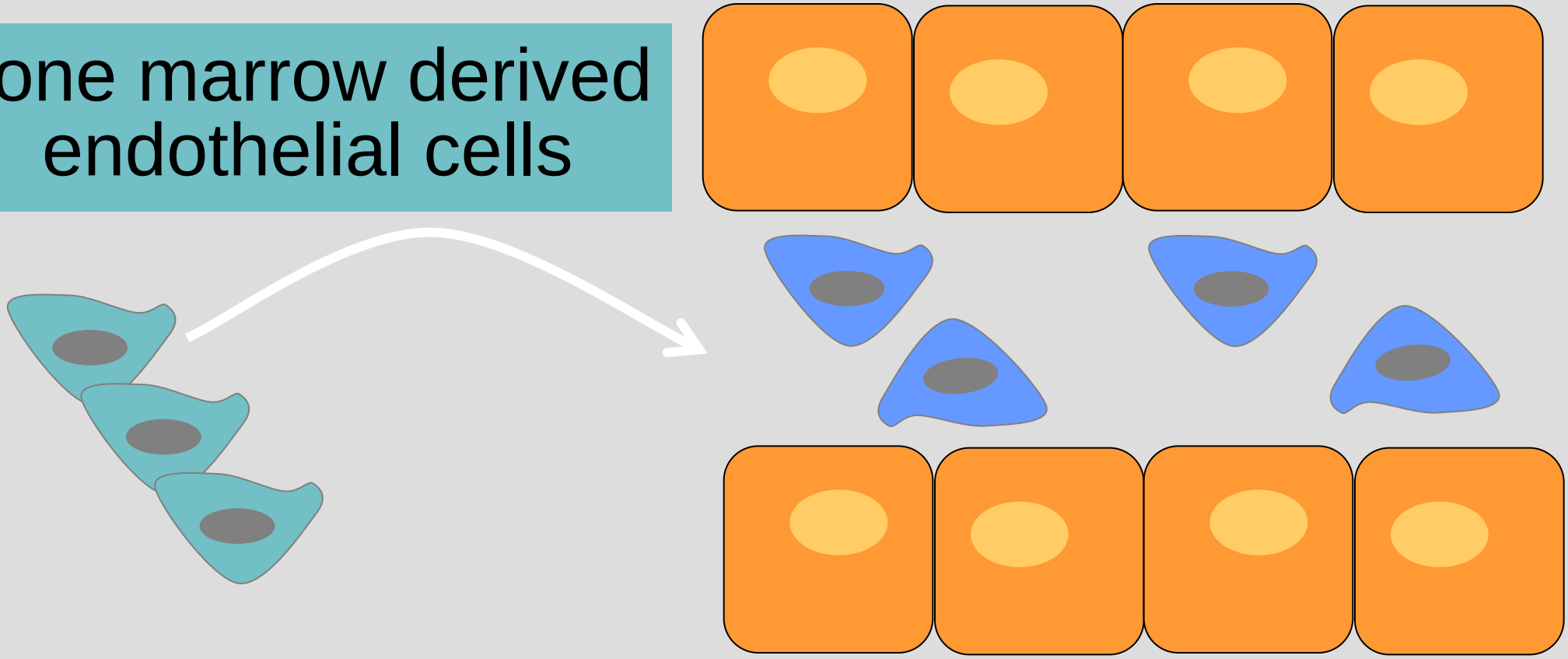
Monocrotaline rat model for VOD/SOS



DeLeve, L. Semin Liver Dis 2007

Monocrotaline rat model for VOD/SOS

Bone marrow derived endothelial cells



Harb, Gastroenterology 2009

Pyrrolizidine Alkaloids : From VOD to SOS

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  RBC in the space of Disse
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A discrete clinical, epidemiologic and pathologic entity

VOD/SOS and Pyrrolizidine Alkaloids Open Issues

- Low-level dietary exposure to PA
- Toxic injury from multiple agents : Hirmi Valley disease (DTT + PA)
- Contaminated herbal remedies
- Serum pyrrole-protein adducts as biomarkers for increased exposure

Edgar, Chem Res Toxicol 2014. Robinson, J Hepatol 2014. Lin, J Hepatol 2011

SOS in Hepatology

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VOD/SOS and HSCT

Diagnosis/definition

weight gain - tender hepatomegaly – jaundice

within 3 weeks of HSCT

Differential diagnosis

- Underlying liver disease
- Iron overload
- Cardiac dysfunction
- G*vs*HD
- DILI
- Sepsis

A non-specific clinical syndrome

Liver Biopsy and HSCT related VOD/SOS

Clinically suspected SOS	Biopsy proven SOS
Yes	15/26 (58%)
No	2/33 (6%)

Carreras E, Bone Marrow Transplant 1993

HSCT related VOD/SOS

- Incidence 5,3% (0% - 53%)
- Case fatality rate 18,4% (3% - 47%)
- Severity
  - Self limited 8%
  - Complete resolution ‘with therapy’ 64%
  - Fatal/unresolved by day 100 28%

Carreras, Blood 1998 1652 HSCT in 73 centers – Nov 1995 - March1996

Risk factors for HSCT related VOD/SOS

Risk factors	RR
Allogeneic HSCT	2.8
High dose cytoreductive therapy	2.3
Prior abdominal irradiation	2.9
AST	2.4
Karnofsky PS < 90%	2.7

Carreras, Blood 1998

Treatment for HSCT related VOD/SOS

Proposed prophylaxis

- Anticoagulation
- Ursodiol
- Antithrombin
- Defibrotide

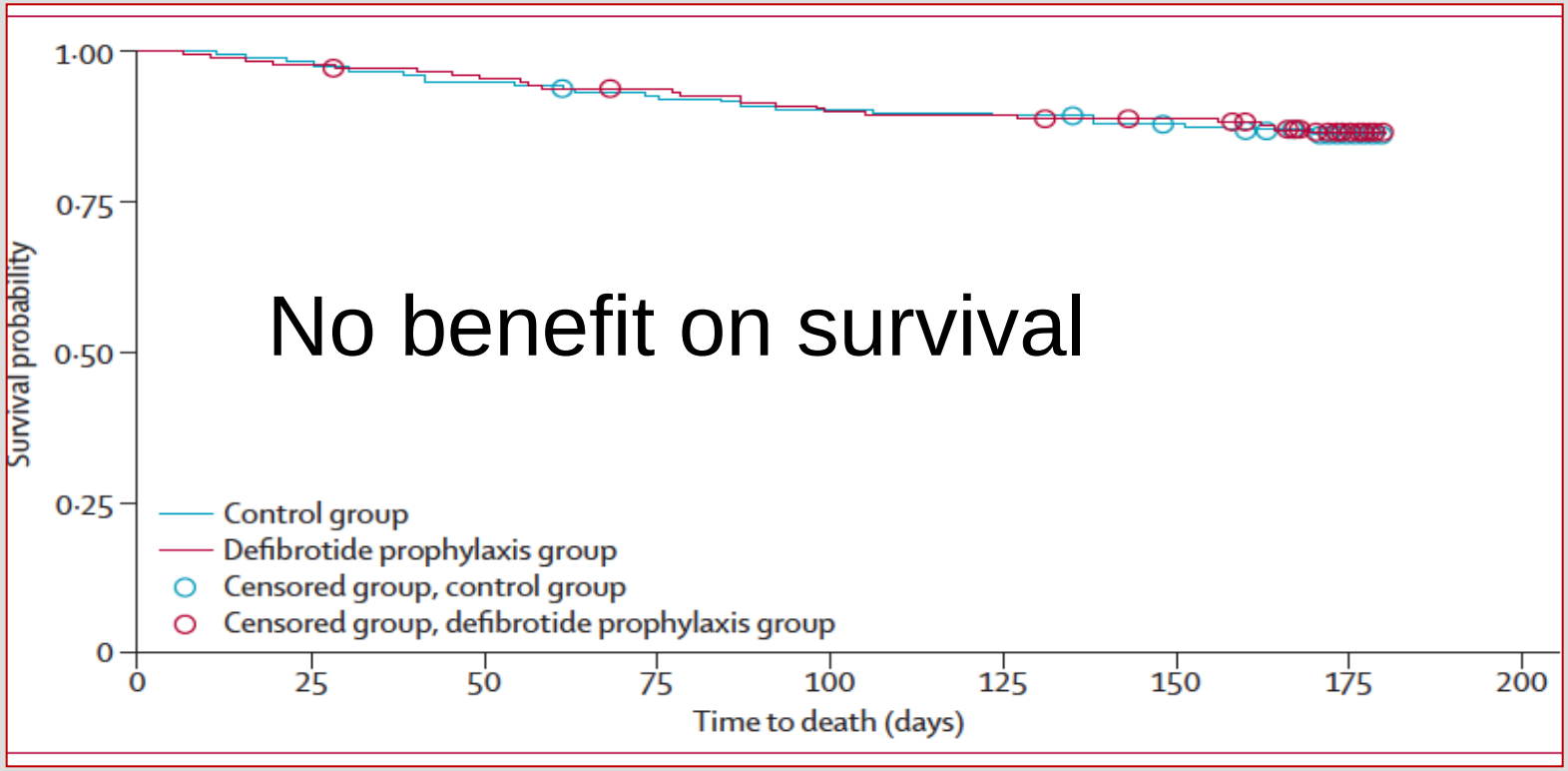
Proposed therapy

- Prostacyclin
- R-TPA
- TIPS
- Defibrotide

Carreras, Blood 1998. Valla, Gut 2008. DeLeve, Semin Liver Dis 2002.

Prevention of VOD/SOS (Day 30)

Defibrotide (25 mg/kg)	Placebo	*P*
12%	20%	0.05



Corbacioglu, Lancet 2012 356 children at high risk of SOS

SOS in Hepatology

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SOS/VOD and Liver Metastasis of CRC

Diagnosis/definition

Sinusoidal changes
in surgically resected specimens

Sinusoidal dilation	30-65%
Perisinusoidal fibrosis	35-40%
Centrilobular fibrosis	30%
Atrophy/regenerative changes	12-20%

Vigano, Ann Surg 2013. Nguyen-Khac, Int J Hepatol 2013

SOS/VOD and Liver Metastasis of CRC

Diagnosis/definition

Sinusoidal changes
in surgically resected specimens

Clinical manifestations	Rare
Postoperative complications	Increased (±)
Response to chemotherapy	Decreased (±)
Survival	Unaffected

A histopathological syndrome. A clinical entity ?

SOS in Hepatology

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Causes for VOD / SOS

Pyrrolizidine alkaloids	Cytosine arabinoside
	Cyclophosphamide*
6-Mercaptopurine	Dacarbazine
6-Thioguanine	Gemtuzumab-ozogamicin
Actinomycin D	Melphalan*
Azathioprine	Oxaliplatin
Busulfan*	Urethane

Causes for VOD / SOS

Pyrrolizidine alkaloids

Only toxic exposure !

6-Mercaptopurine

6-Thioguanine

Actinomycin D

Azathioprine

Busulfan*

Cytosine arabinoside

Cyclophosphamide*

Dacarbazine

Hepatic metabolism

Gemtuzumab-ozogamicin

Melphalan*

Bone marrow toxicity

Oxaliplatin

Urethane

SOS in Hepatology – Key Messages

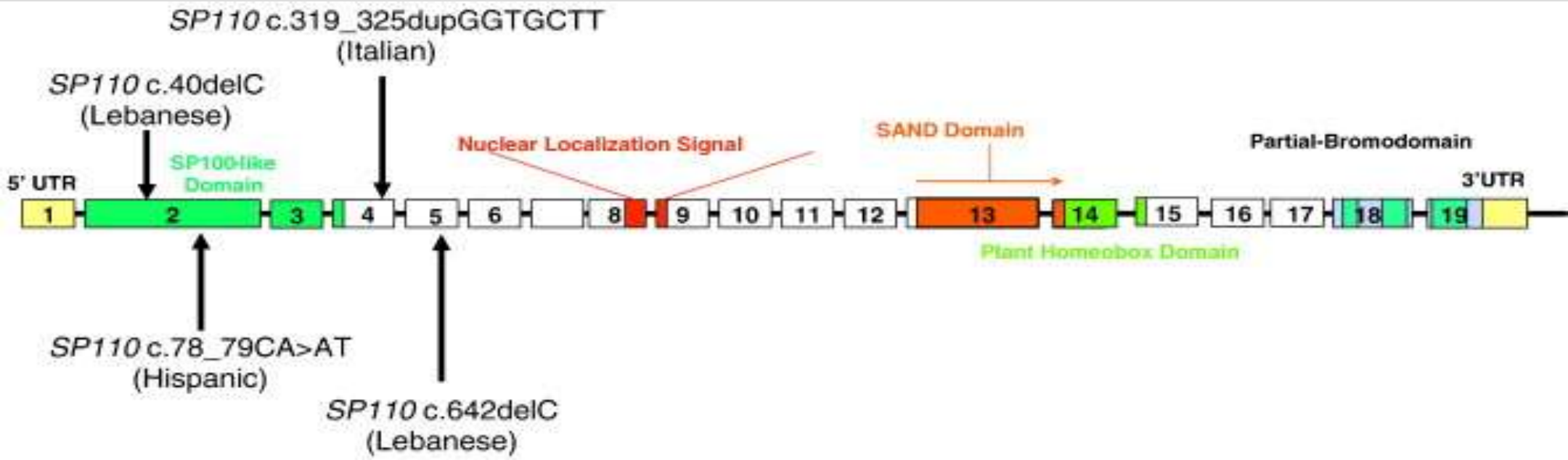
- Dose-dependent toxicity to sinusoidal endothelium. Restoration by bone marrow derived endothelial cells likely crucial.
- Myeloblative therapy and anticancer agents as the most common factors.
- A difficult diagnosis, in the absence of liver biopsy. Relevance of sole histopathological changes to be clarified.
- Limited means available for prophylaxis and treatment except for reduced exposure.

Oxaliplatin and Sinusoidal Dilation

Study	*n* of patients	Sinusoidal dilation
Vauthey et al. [26]	79	15 of 79 patients (19%)
Mehta et al. [36]	70	43 of 70 patients (61%)
Alioa et al. [40]	52	10 of 52 patients (19%)
Kandutsch et al. [37]	47	11 of 47 patients (23%)
Rubbia-Brandt et al. [35]	43	34 of 43 patients (78%)
Pawlik et al. [33]	31	3 of 31 patients (10%)
Nakano et al. [42]	90	38 of 90 patients (42%)

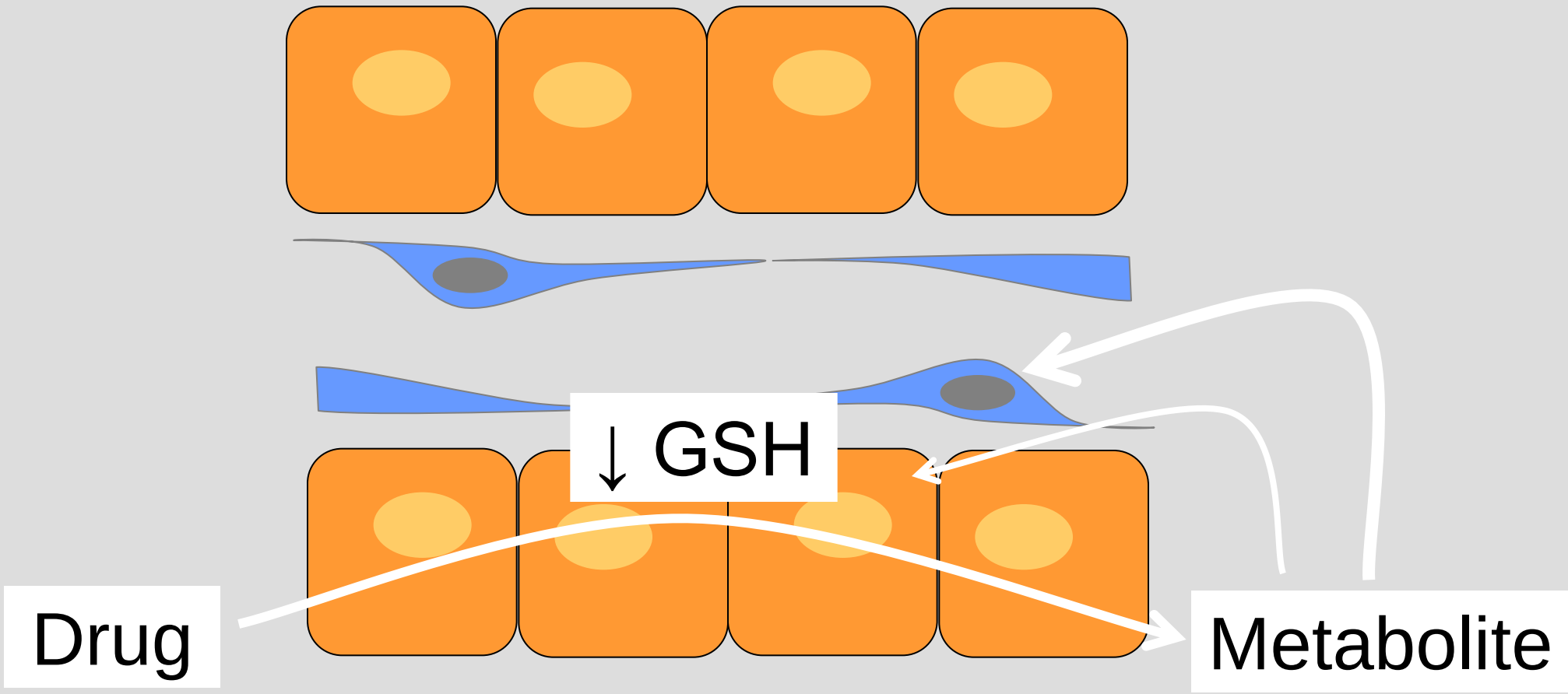
Cleary, J. M. et al. Oncologist 2009;14:1095-1105

Hepatic VOD with immunodeficiency (VODI)



Wang, T. Clinical Immunology, 2012

VOD / SOS



DeLeve, L. Semin Liver Dis 2007

Pyrrolizidine Alkaloids Tajikistan, 1992

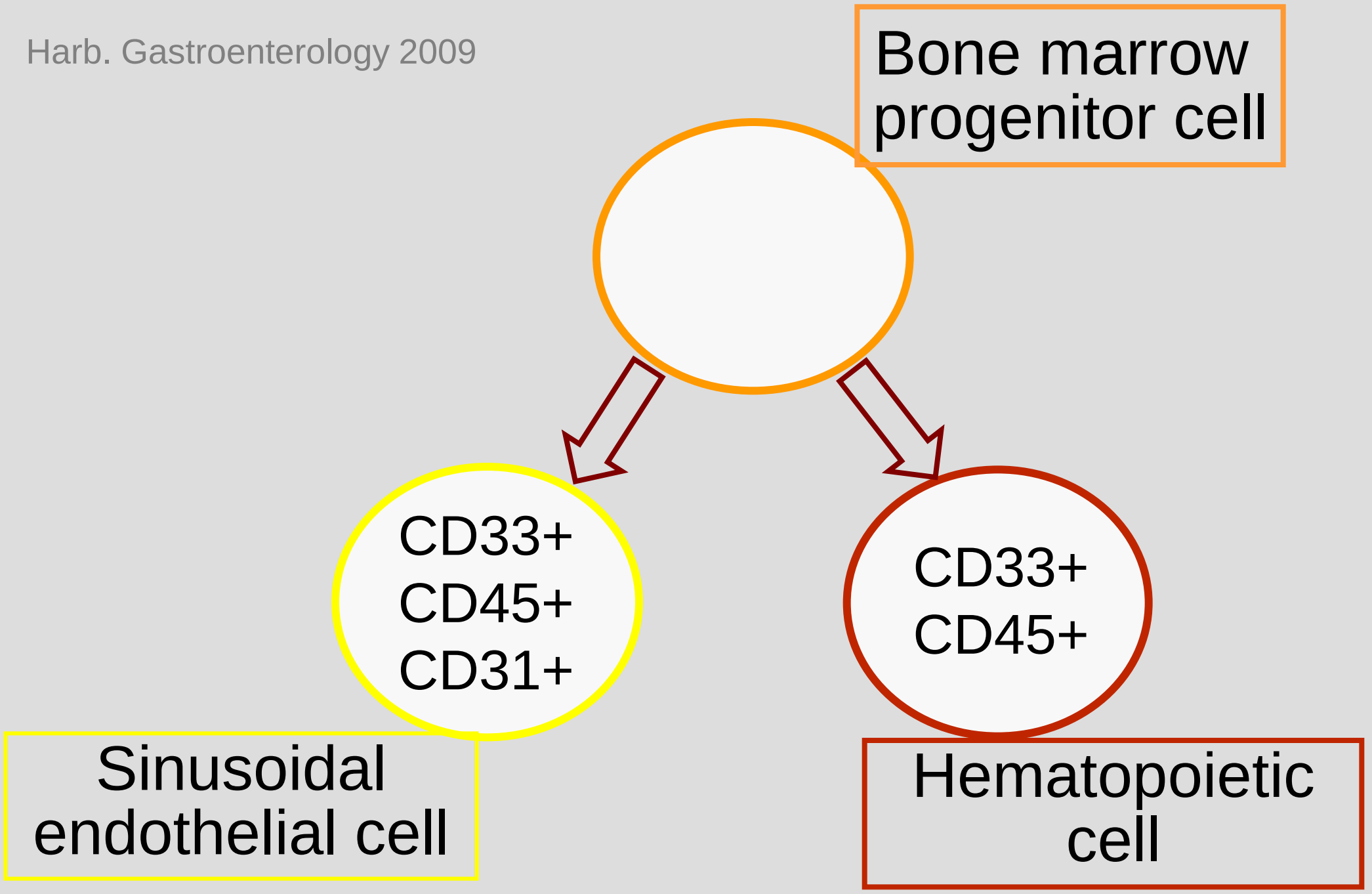
- 1st case: 6 weeks after 1st consumption
- By March 1993: Attack rate 4% (3906 cases)
  Case fatality ratio 1.3%
- Stage 1 (55.5%) abdominal pain, vomiting
  2 (29.9%) hepatomegaly
  3 (13.7%) ascites
  4 (0.9%) encephalopathy

Chauvin, Santé, 1994

VOD and Hematopoietic Stem Cell Transplantation

Seattle criteria	Baltimore criteria
2 of 3 findings within 20 days of transplantation	Hyperbilirubinaemia + 2 other criteria
Bilirubin >34.2 µmol/l	Bilirubin >34.2 µmol/l
Hepatomegaly or painful liver	Hepatomegaly, usually painful
>2% weight gain (fluid accumulation)	> 5% weight gain Ascites

Harb. Gastroenterology 2009



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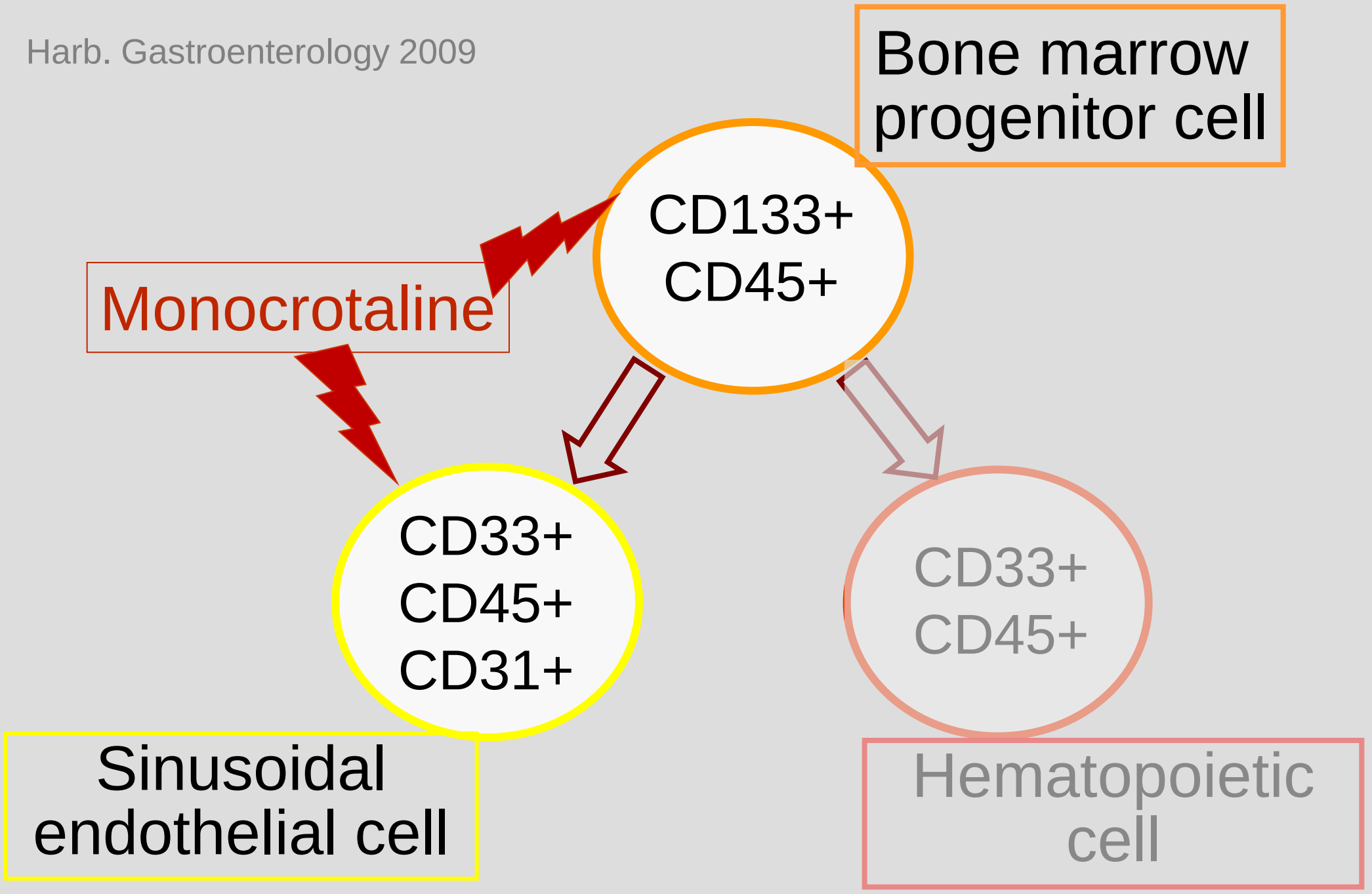
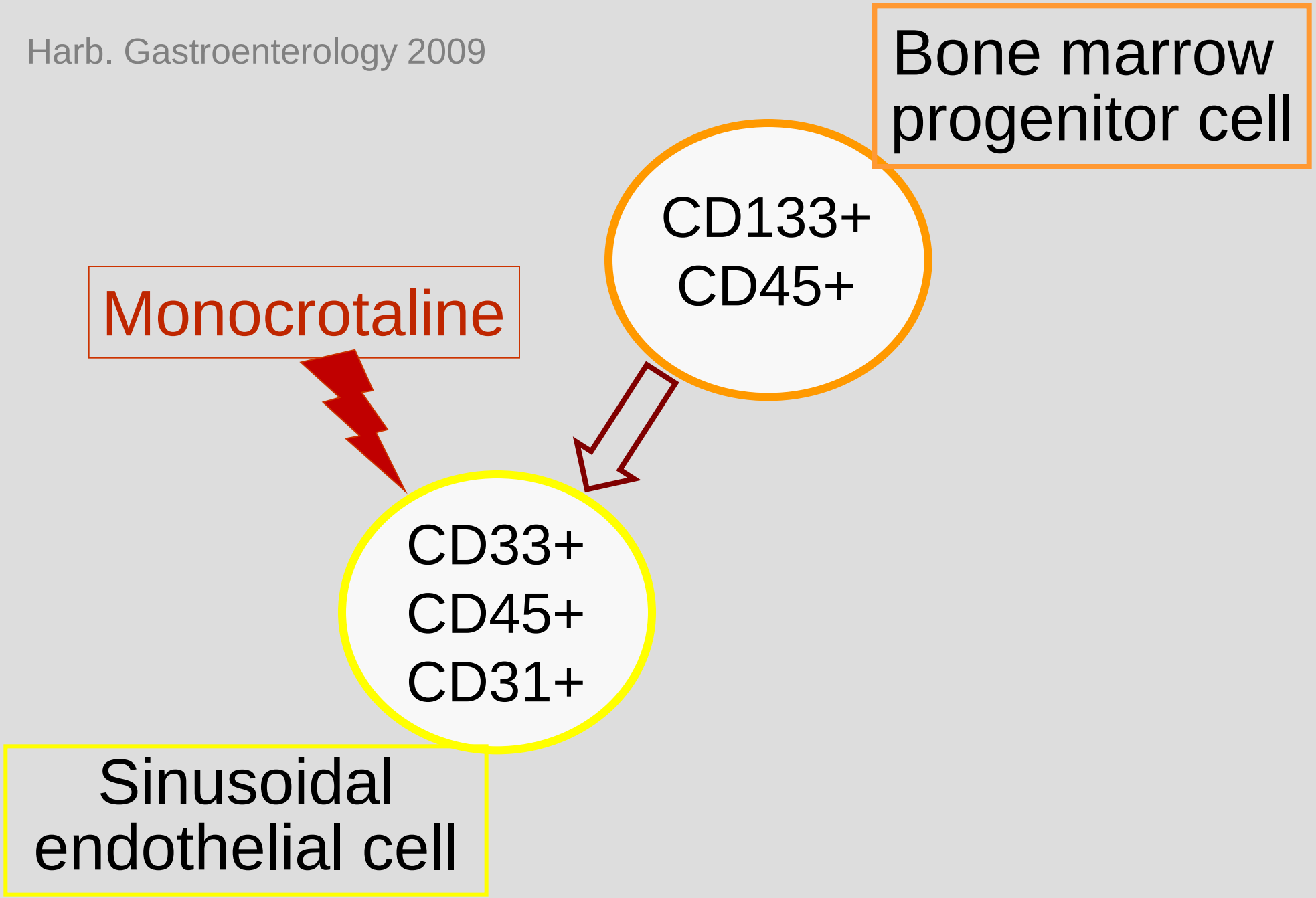


Harb. Gastroenterology 2009



Pyrrolizidine Alkaloids : From VOD to SOS

Monocrotaline rat model (1999)

→ A primary injury to sinusoidal endothelium
→ Toxic metabolites produced in hepatocytes
Greater depletion in GSH in endothelium
→ Decreased NO, increased MMP2 & MMP9
→ Defective replacement of sinusoidal/venous endothelial cells with bone marrow derived endothelial progenitors

DeLeve, L. Semin Liver Dis 2007 Harb. Gastroenterology 2009

TV Liver Biopsy for Post-HSCT Liver Dysfunction Beaujon

Ascites	HVPG (mm Hg)	Histopathology
Moderate	10	Infiltration
Moderate	6	VOD/SOS
Moderate	11	Fatty liver
Absent	10	Fatty liver
Moderate	6	Fatty liver

Rautou, PE unpublished data

HVPG and HSCT related SOS/VOD

	HVPG ≥ 10 mmHg
SOS/VOD	14/17 (82%)
G*vs*HD	0/15 (0%)

Carreras E, Bone Marrow Transplant 1993