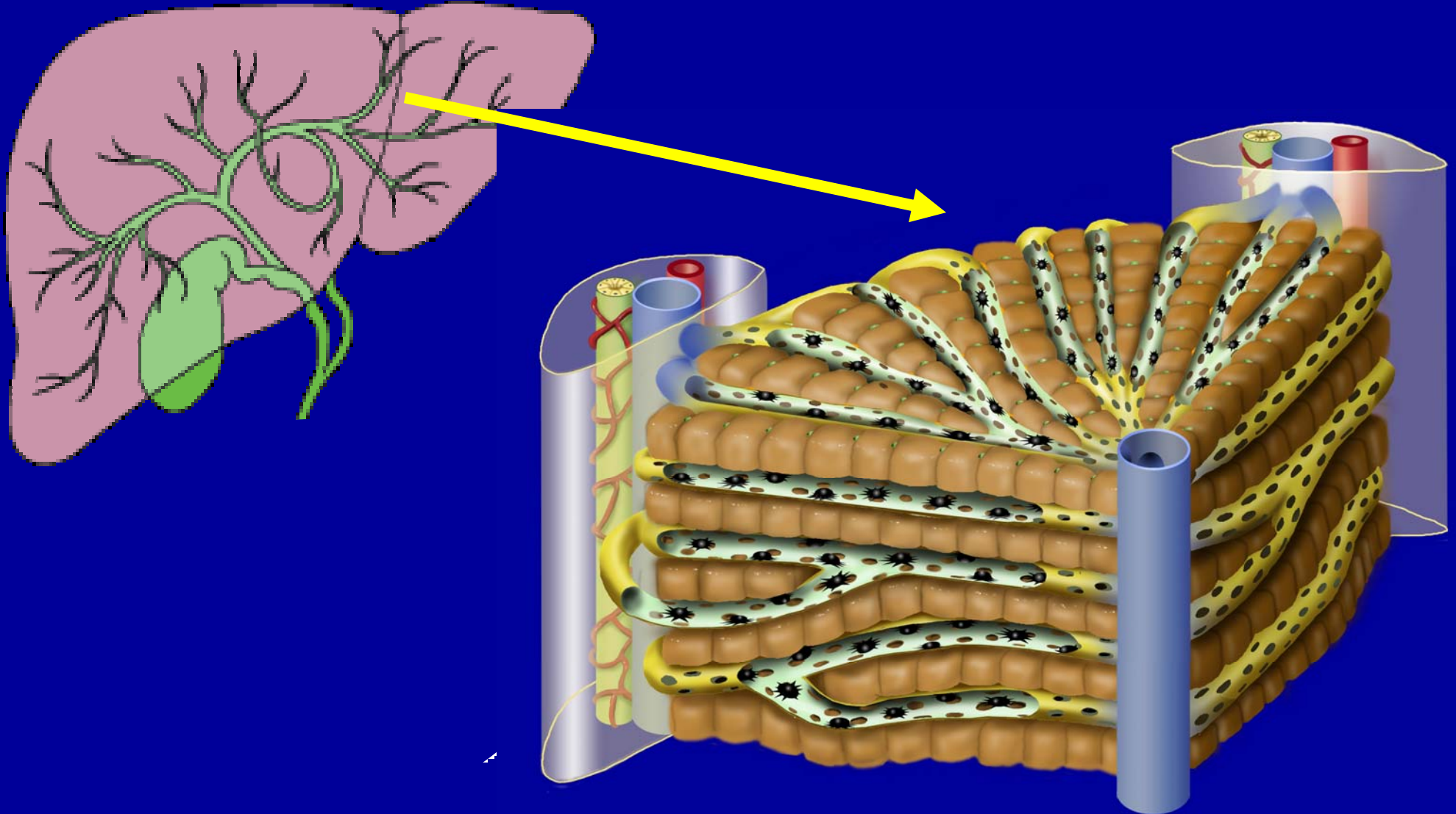


Immunology of Primary Sclerosing Cholangitis

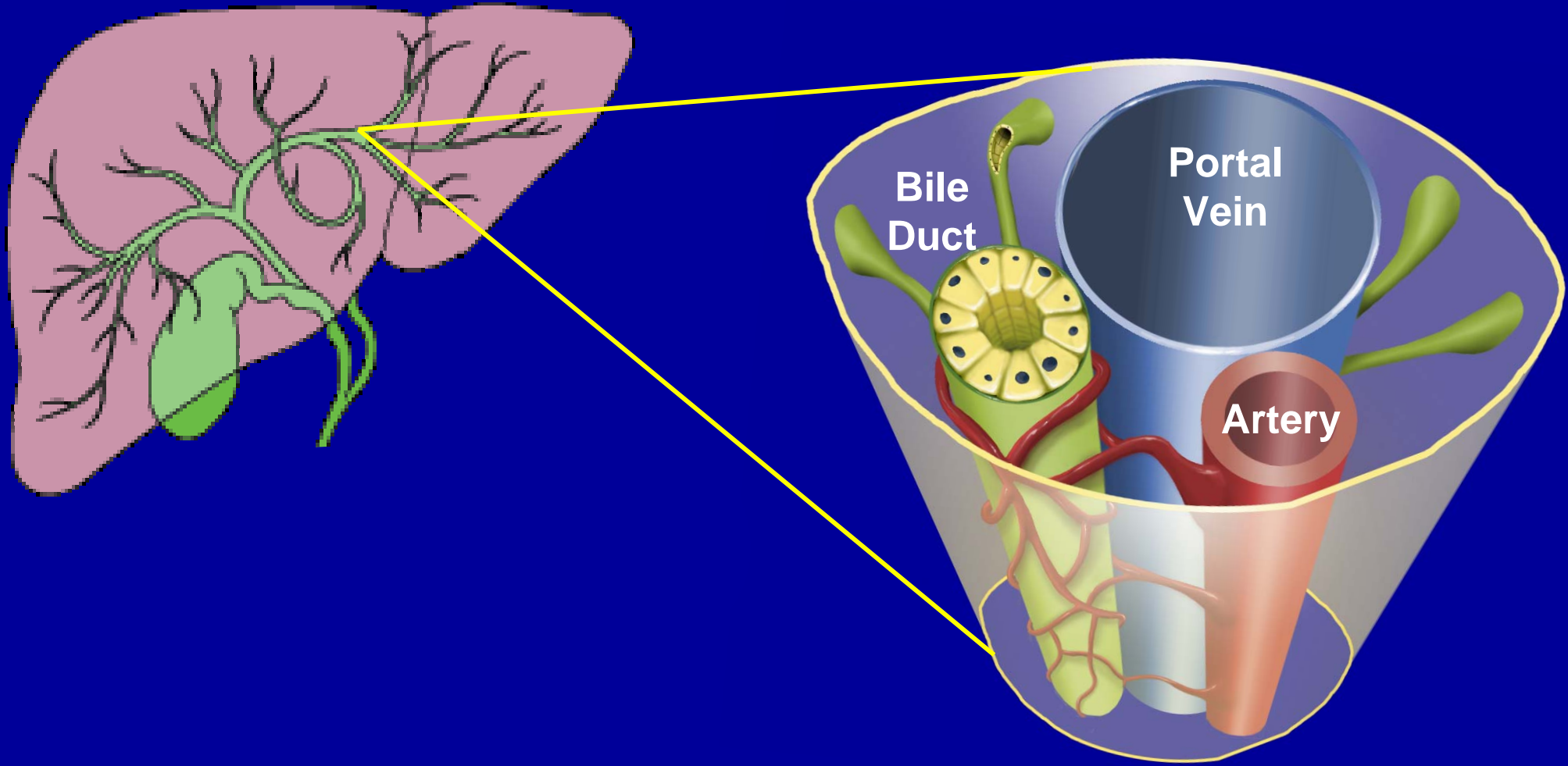
**John M. Vierling, M.D., F.A.C.P.
Professor of Medicine and Surgery
Director, Baylor Liver Health
Chief of Hepatology
Baylor School of Medicine**

**Director of Advanced Liver Therapies
St. Luke's Episcopal Hospital
Houston, TX**

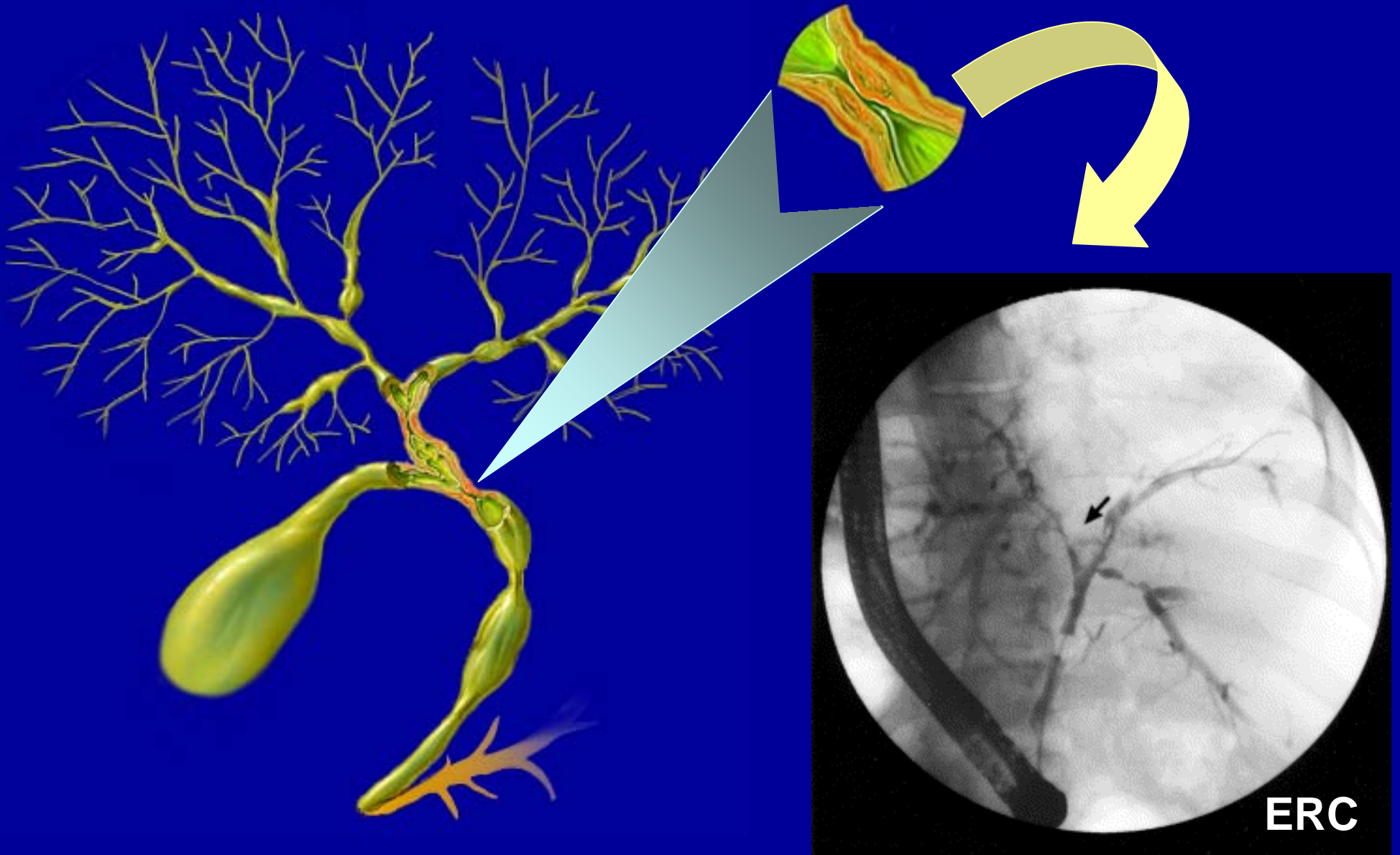
Anatomy of Bile Ducts



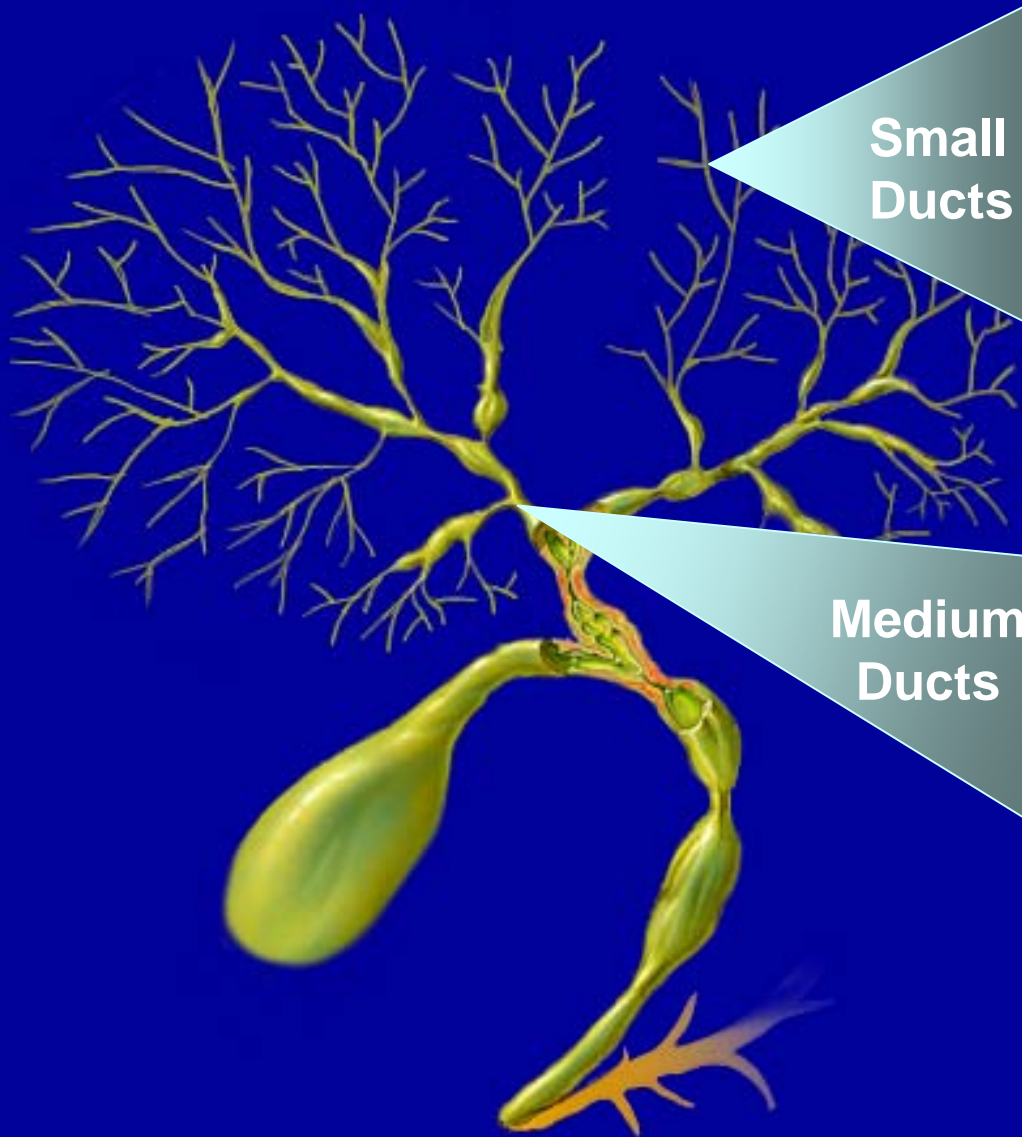
Anatomy of Bile Ducts



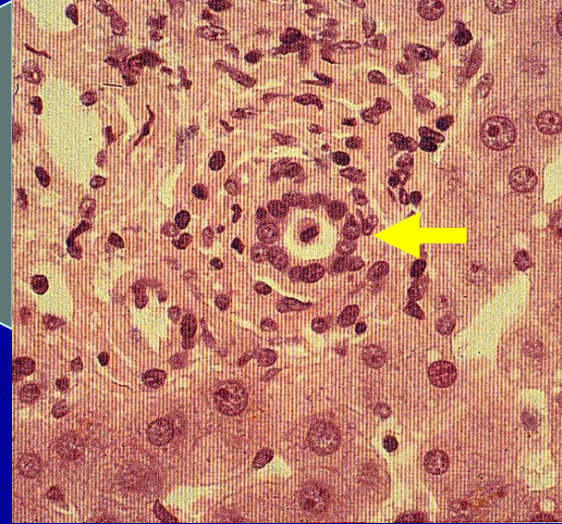
Pathology Primary Sclerosing Cholangitis



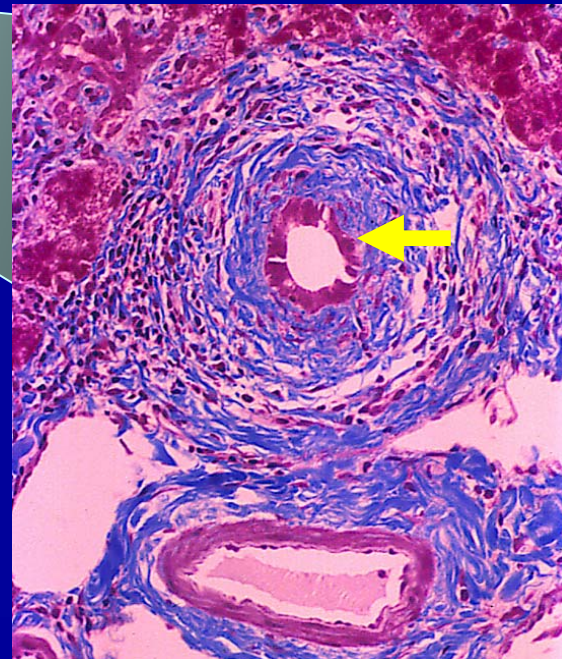
Pathology of Primary Sclerosing Cholangitis



Small
Ducts

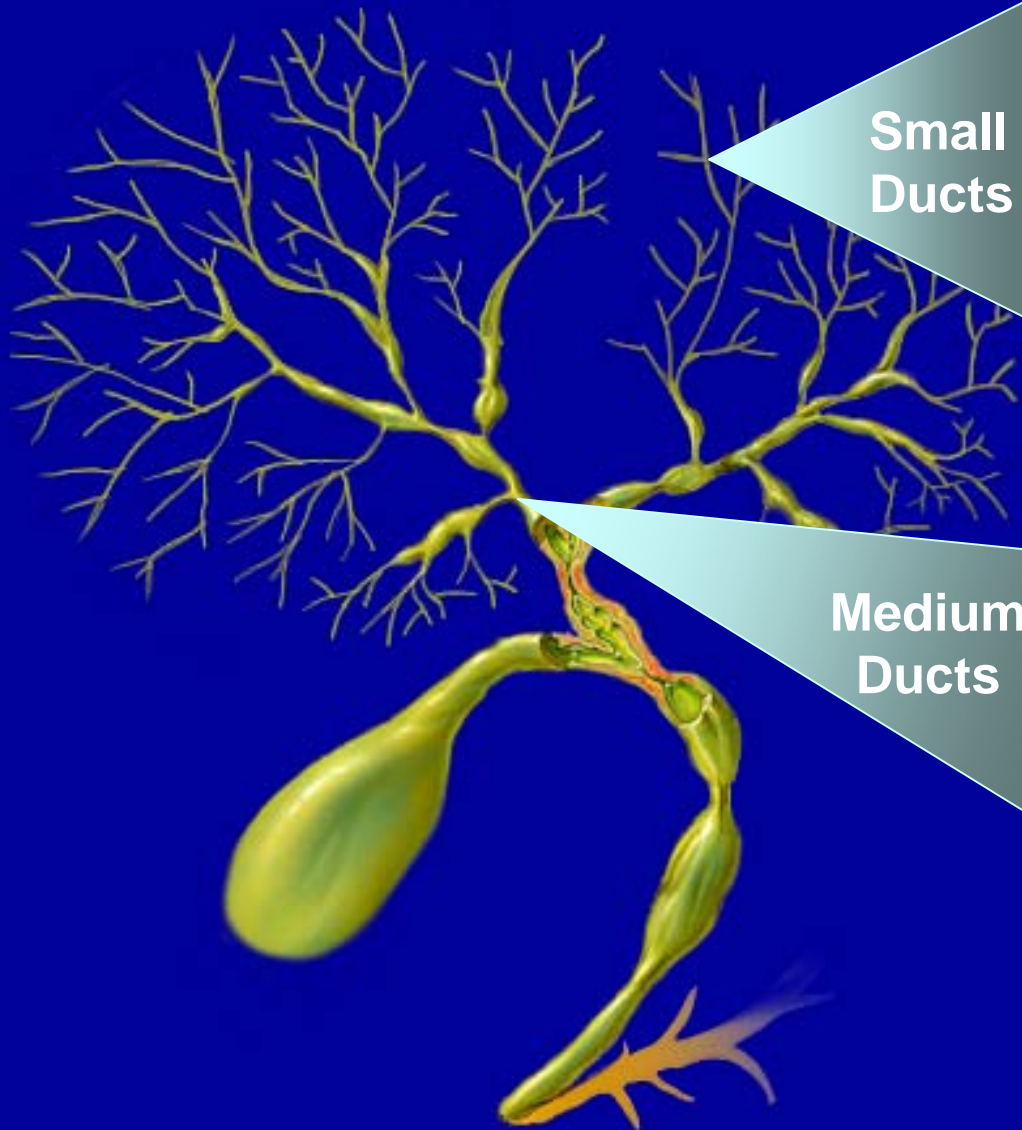


Medium
Ducts

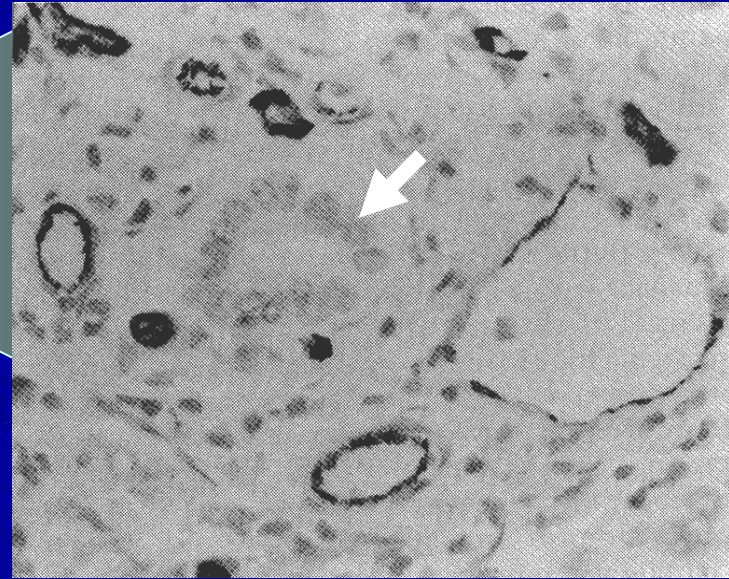


Pathology of Primary Sclerosing Cholangitis

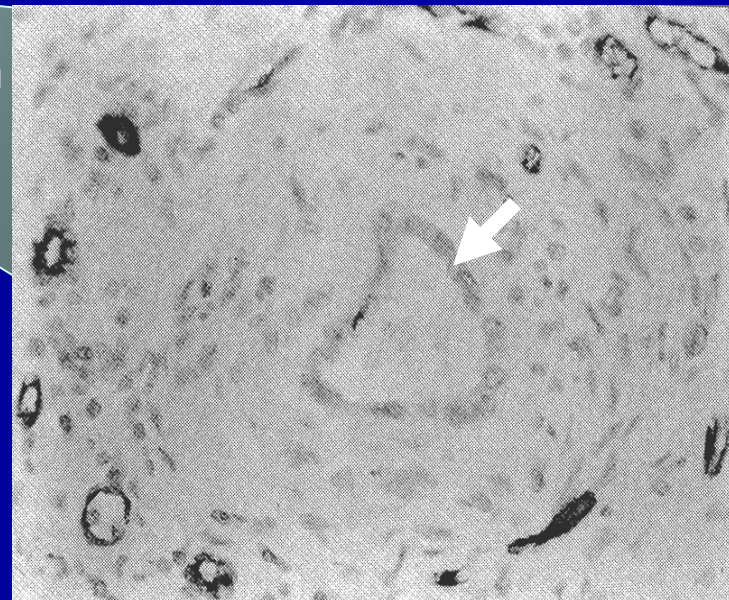
Blood Vessels Pushed Away from Bile Ducts



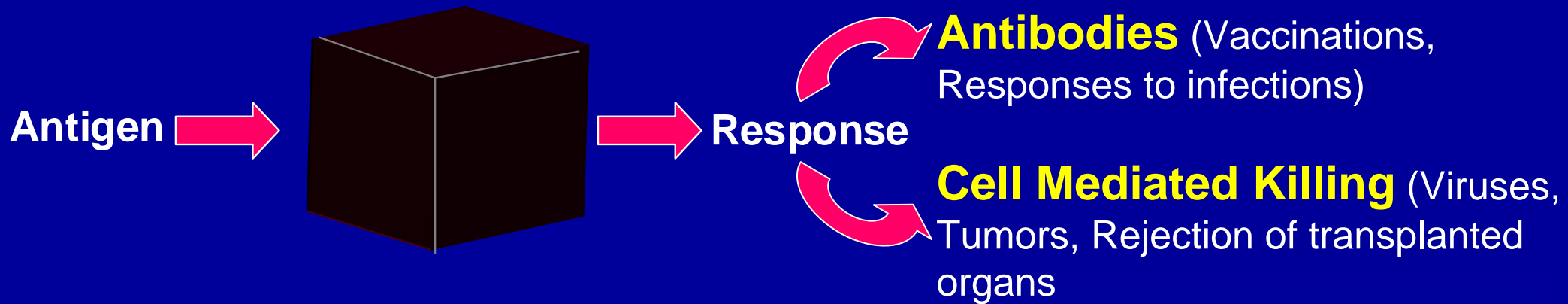
Small
Ducts



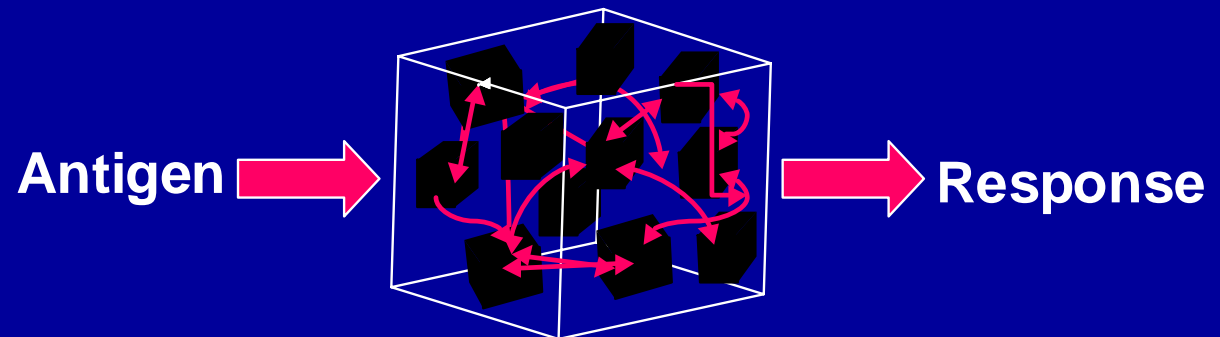
Medium
Ducts



Past



Present



Immunology of Primary Sclerosing Cholangitis

The Three “Rs”

Your immune response has 3 functions:

- Recognize
- Respond
- Remember

Immunology of Primary Sclerosing Cholangitis

Your immune response:

- Recognize:
 - Foreign antigens
 - Avoid self antigens (autoantigens)

Immunology of Primary Sclerosing Cholangitis

Your immune response:

- Respond:
 - Innate immune response
 - Immediate “ready to go” response
 - Triggered by molecules on bacteria, viruses, tumor cells
 - Influences adaptive immune responses
 - Adaptive immune response

Immunology of Primary Sclerosing Cholangitis

Your immune response:

- Respond:
 - Adaptive immune response
 - Small, processed proteins (antigens)
 - Presentation of antigens by HLA molecules to T cells and B cells
 - Activation of T and B cells to antigens

Immunology of Primary Sclerosing Cholangitis

Your immune response:

- Respond:
 - Important to:
 - Regulate both magnitude and duration
 - Shut off response once it has served its purpose

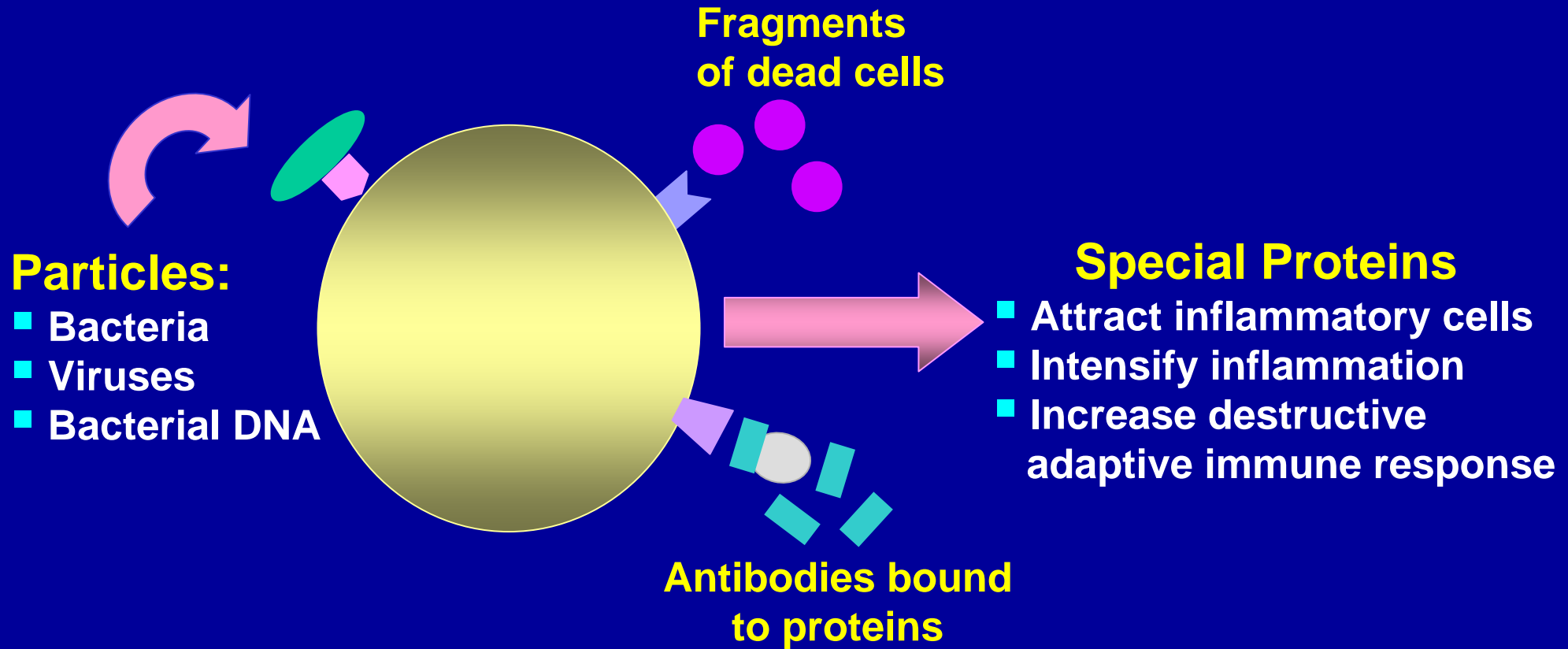
Immunology of Primary Sclerosing Cholangitis

Your immune response:

- Respond:
 - Self or autoantigens= **autoimmunity**
 - Break in self-tolerance
 - As if self were foreign

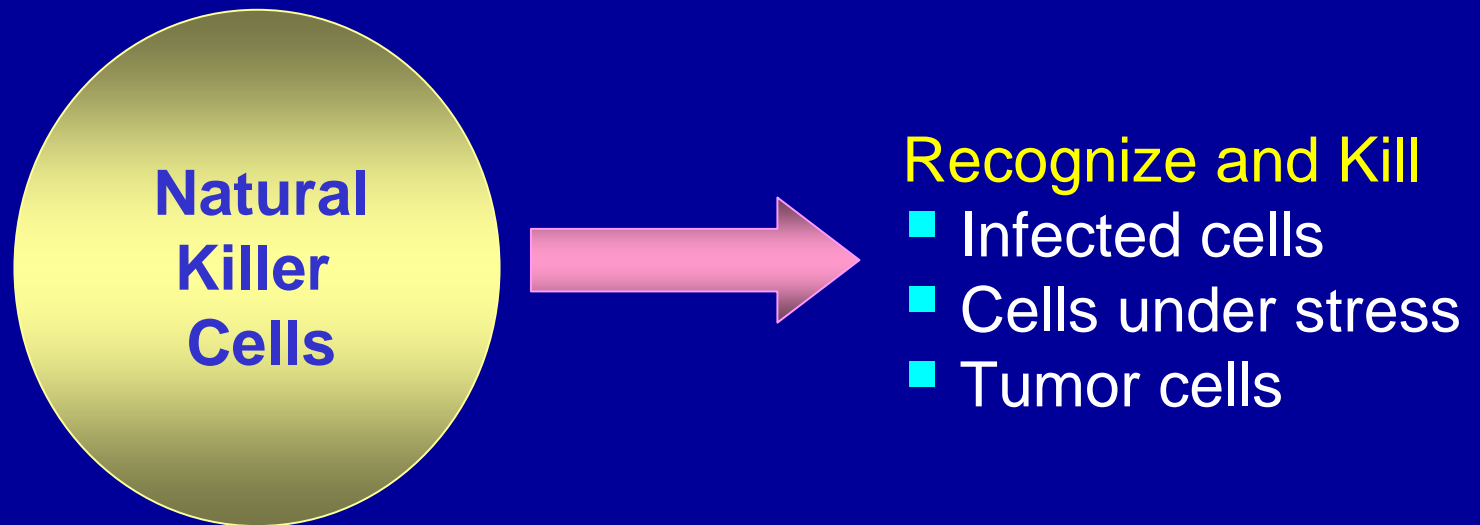
Innate Immune Response

Part One

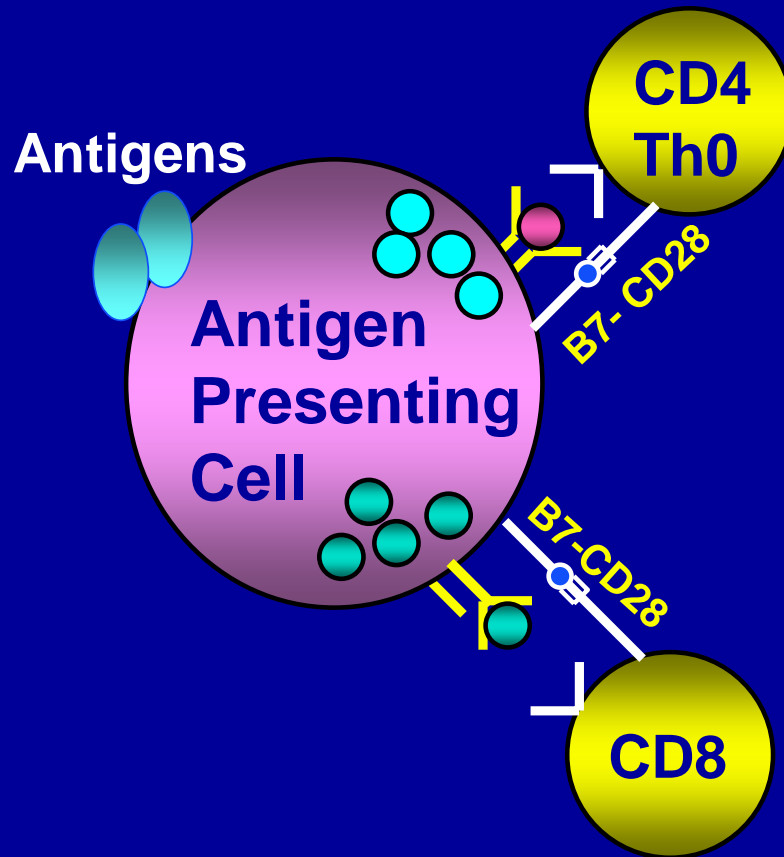


Innate Immune Response

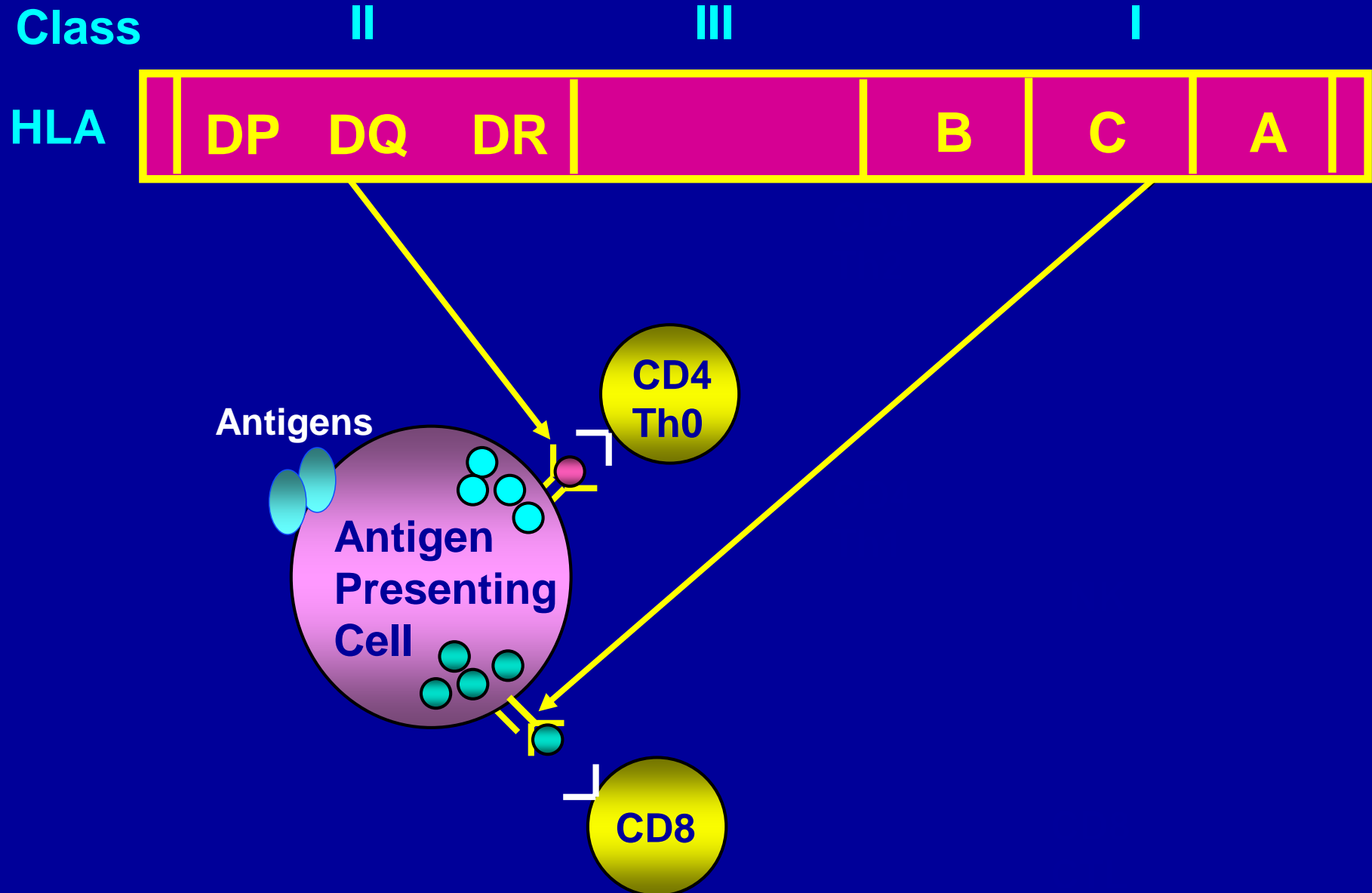
Part Two



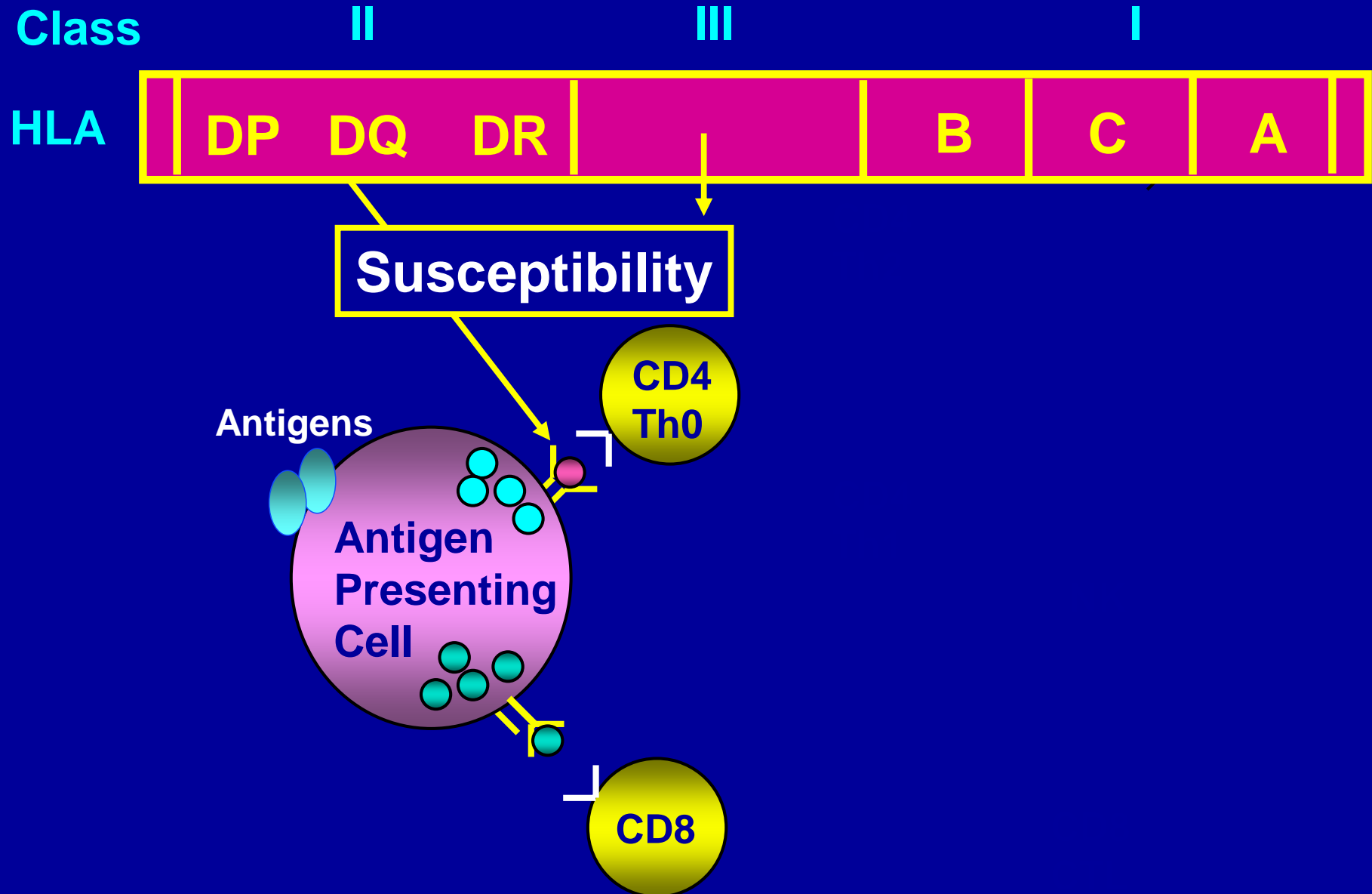
Adaptive Immune Response



Immunogenetics in PSC



Immunogenetics in PSC



Immunogenetics in PSC

Class

II

III

I

HLA

DP

DQ

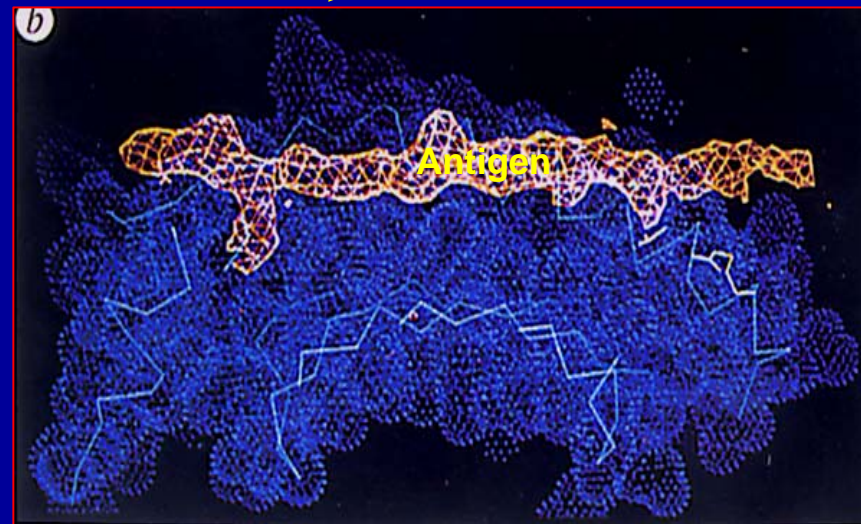
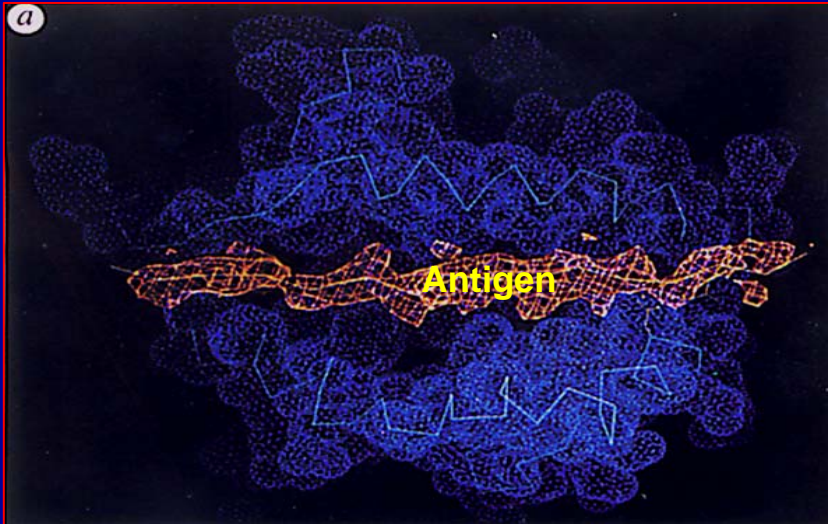
DR

B

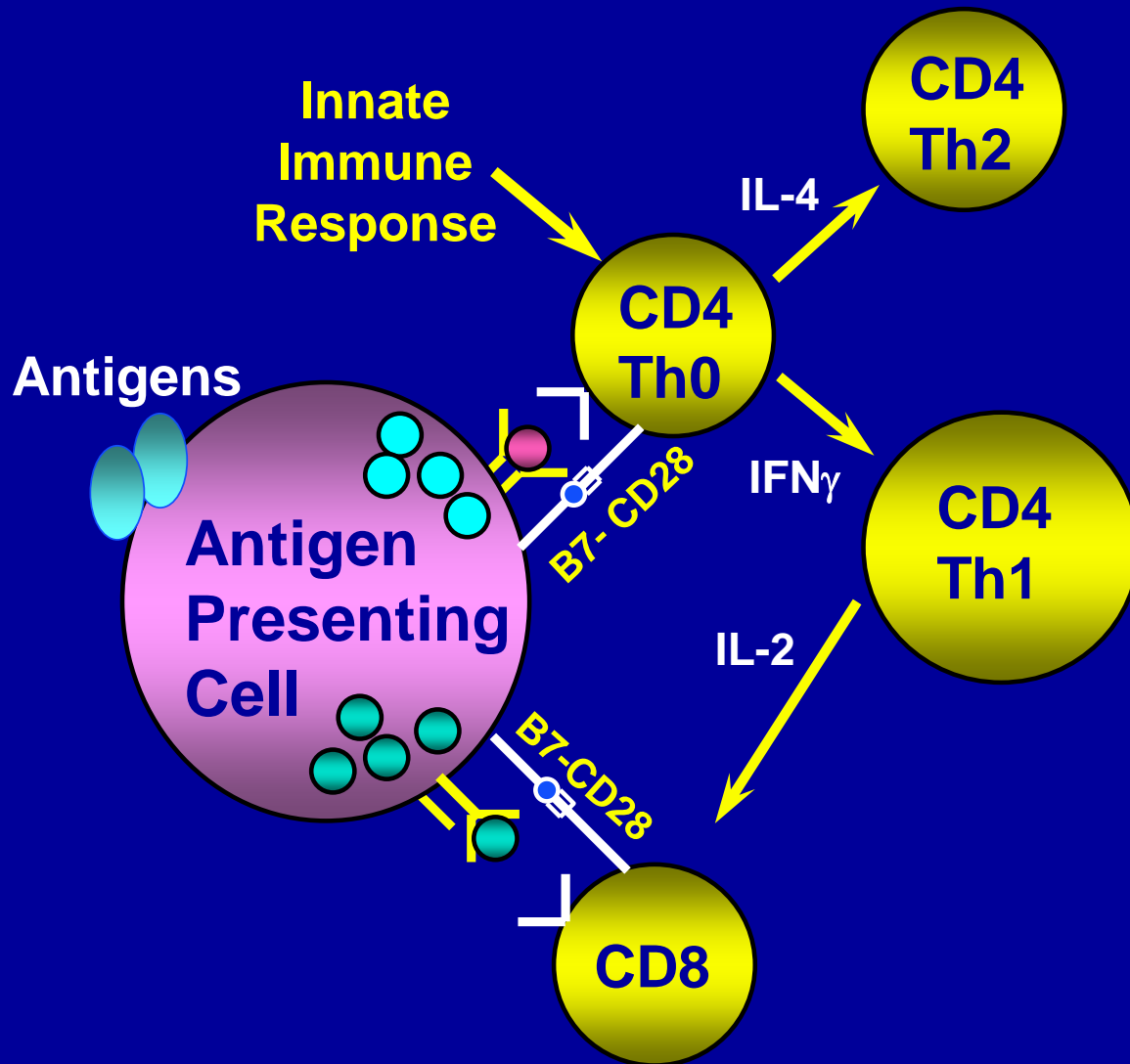
C

A

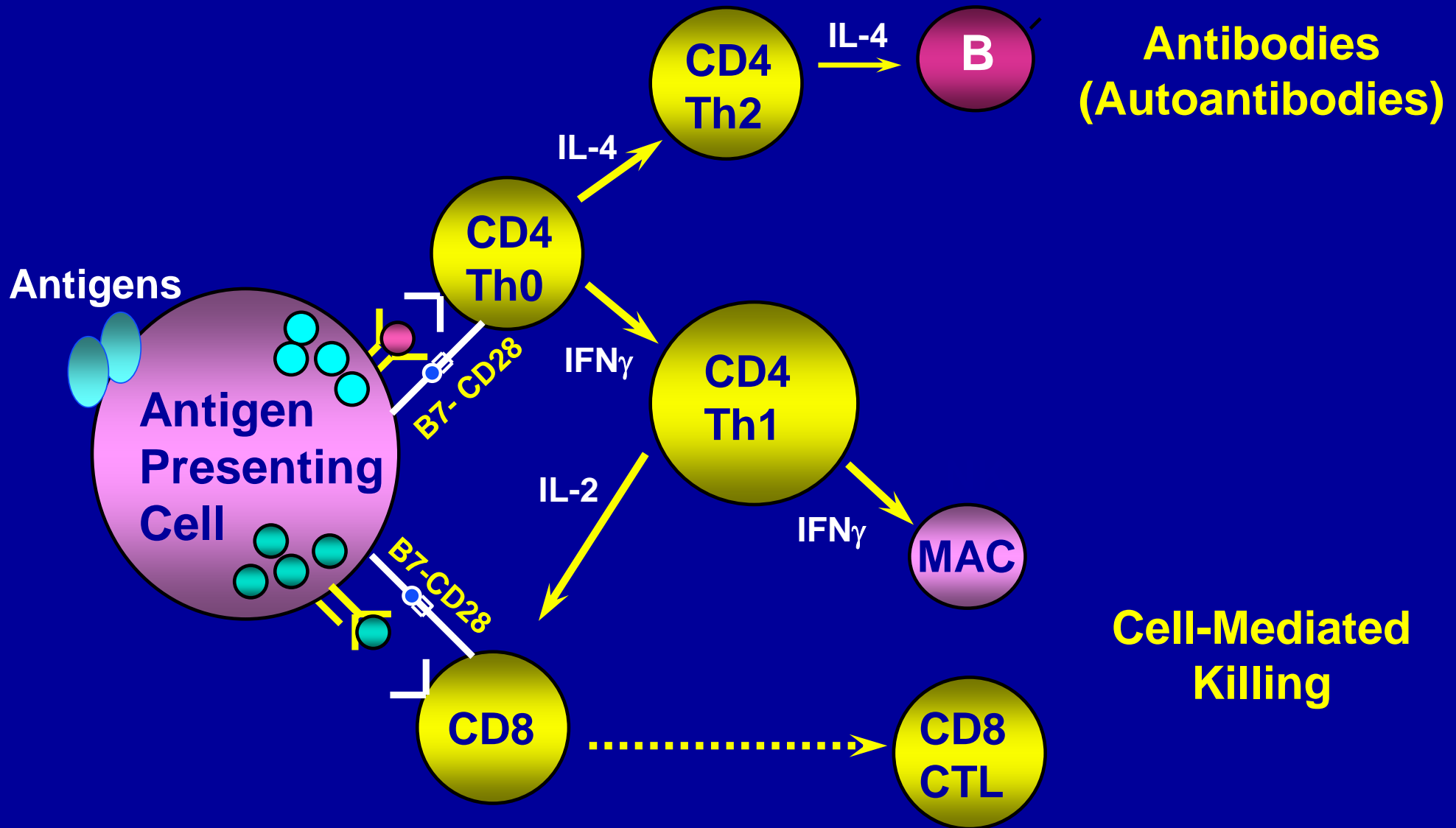
C'4, 2, C4AQ0, MICA, HSPs, TNF α/β



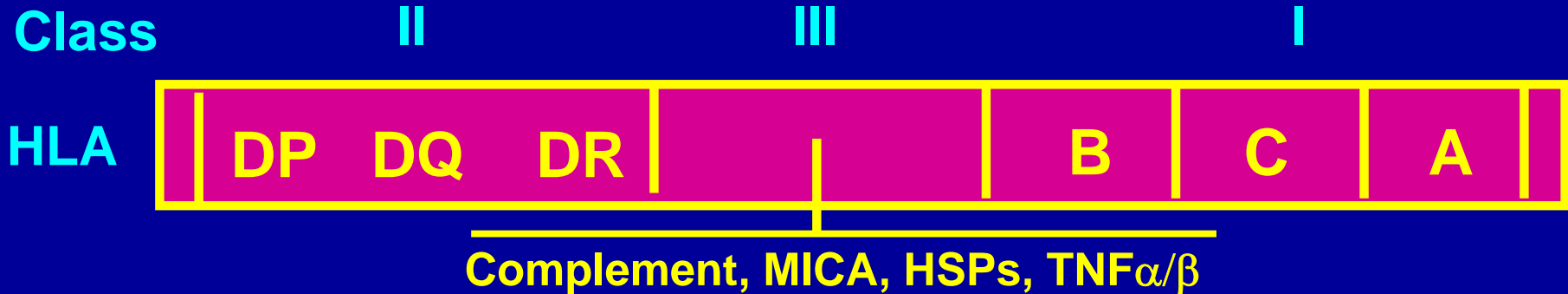
Adaptive Immune Response



Adaptive Immune Response



Immunogenetic Associations in PSC



Susceptibility

	OR
• B8-TNFA*2-MICA*008-DRB3*0101-DRB1*0301-DQA1*0501 DQB1*0201	2.69
• DRB3*0101-DRB1*1301-DQA1*0103-DQB1*0603	3.80
• DRB5*0101-DRB1*1501-DQA1*01102-DQB1*0602	1.52
• MICA*008	5.0

Resistance

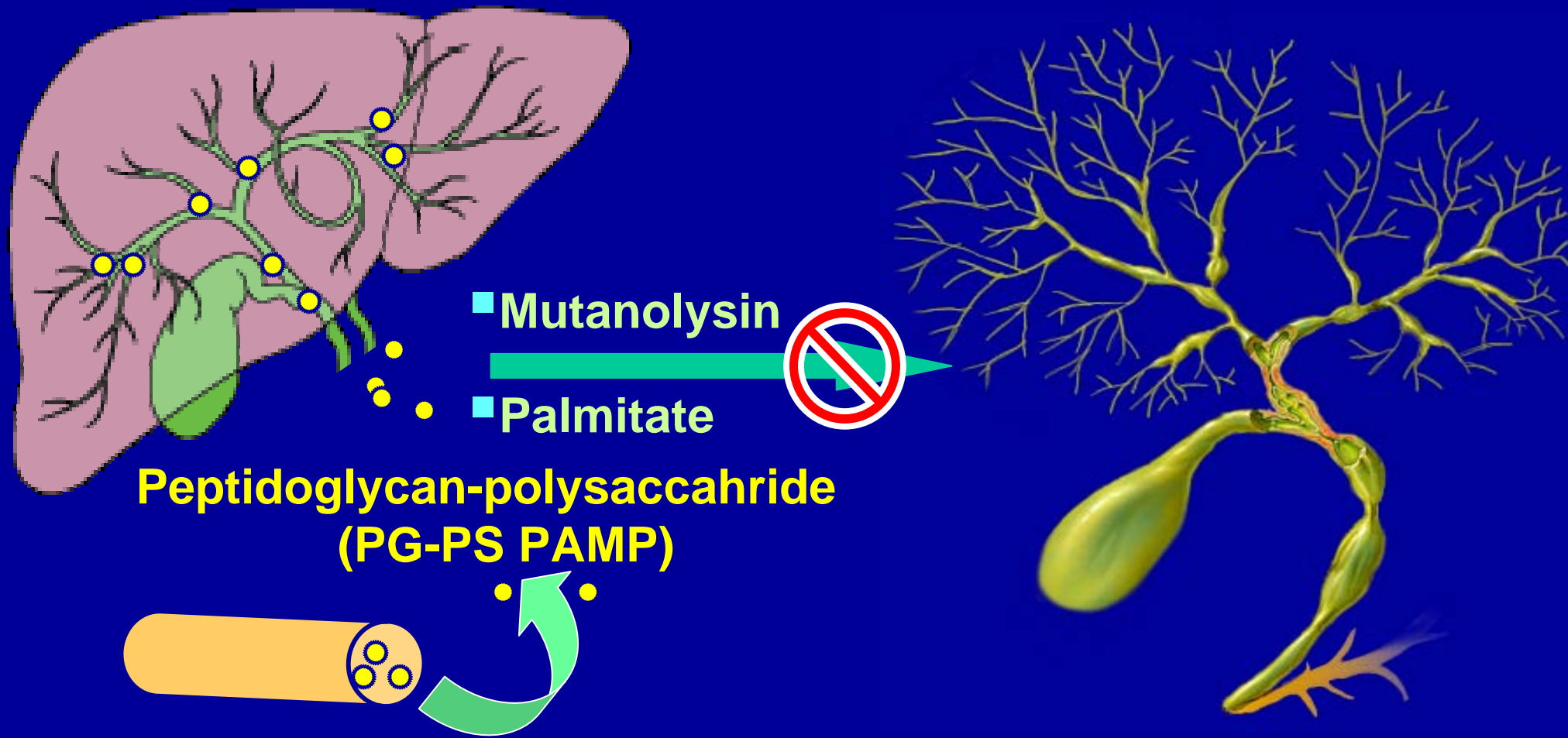
• DRB4*-DRB1*0401-DQA1*0301-DQB1*0302	0.26
• DRB4*-DRB1*0701-DQA1*0201-DQB1*0303	0.15
• MICA*002	0.12

Is PSC an Autoimmune Disease?

Comparison of Classical Autoimmunity and PSC

Classical Autoimmunity	PSC
• Females more than males	No
• Afflicts children & adults	Yes
• HLA susceptibility associations	Yes
• Autoantigen(s)	No
• Autoantibodies or cell-mediated reactions to autoantigens	No
• Associated with other “immune diseases”	Yes
• Responds to immunosuppression treatment	No

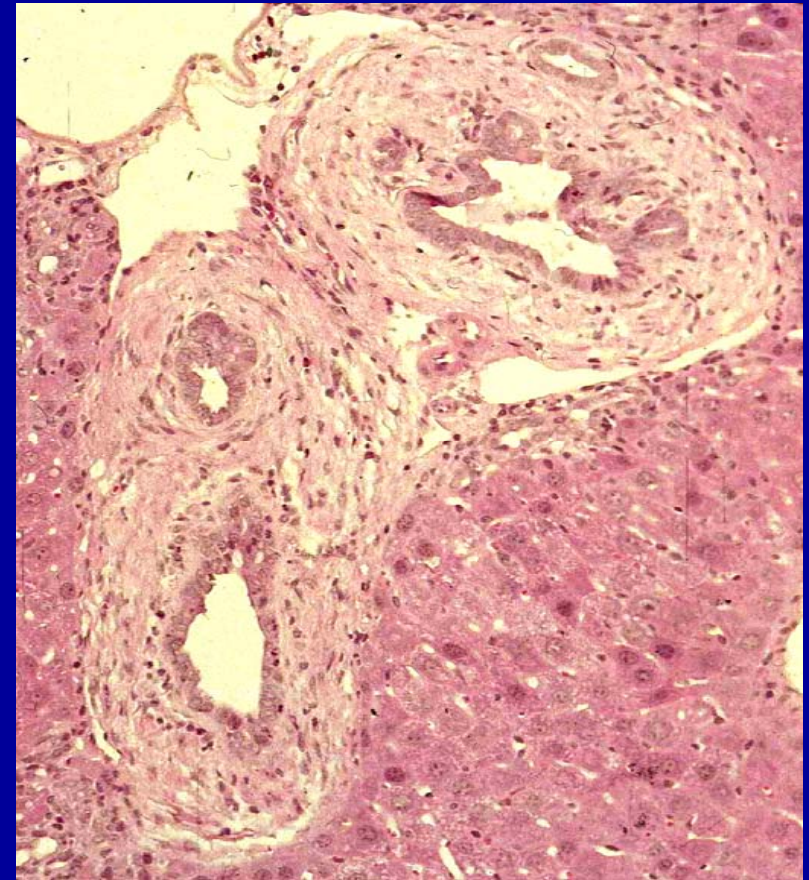
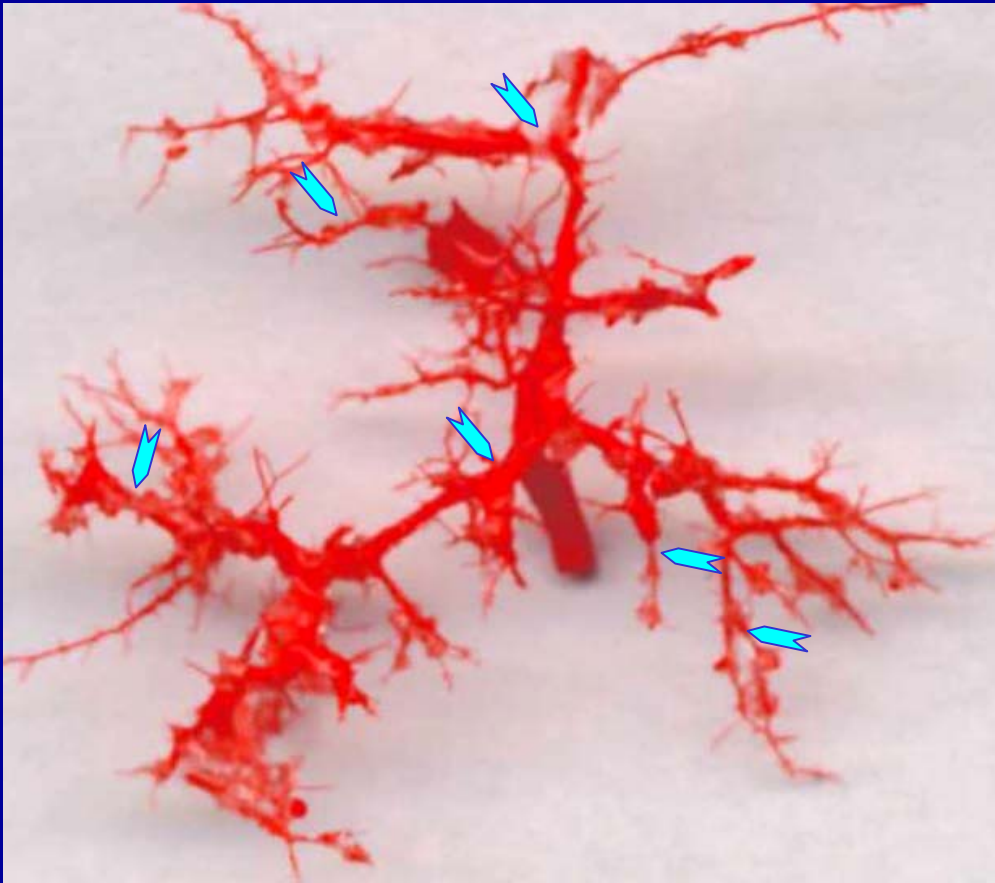
Rat Model of Small Bowel Bacterial Overgrowth



- Small Bowel Overgrowth
- Genetically susceptible rats

Immune Mechanisms in Sclerosing Cholangitis

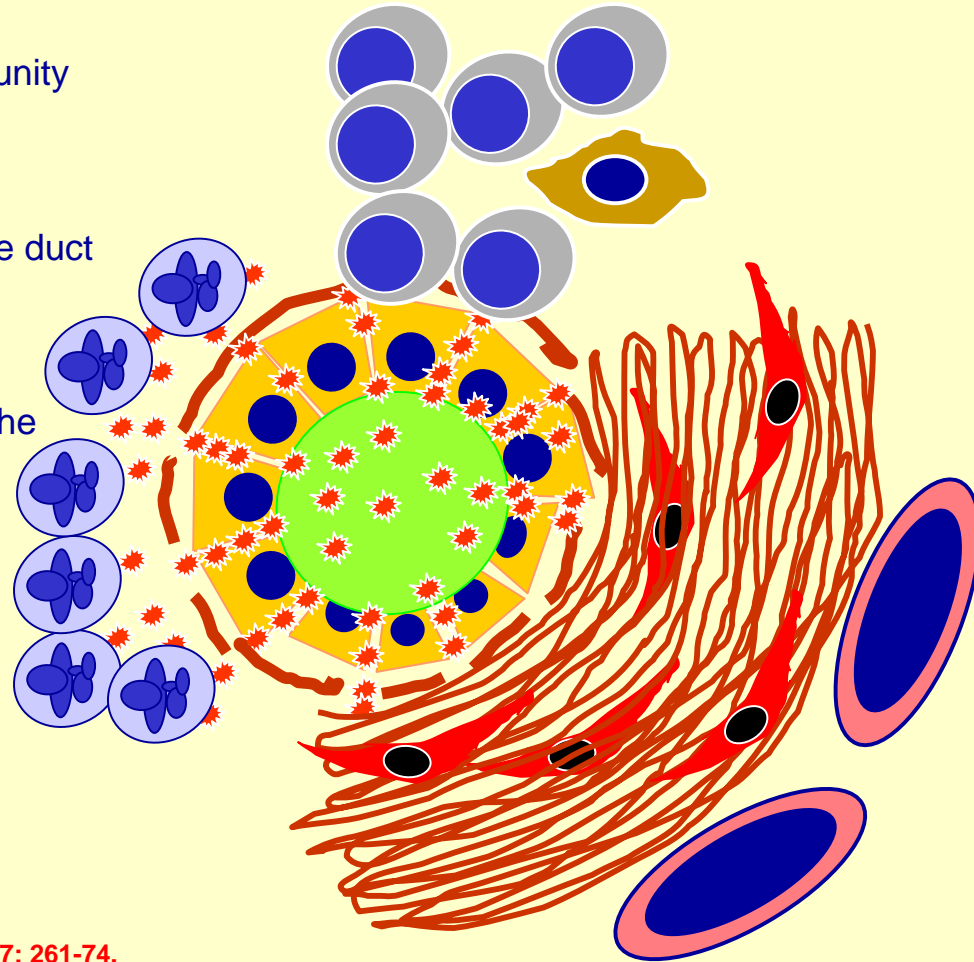
Spontaneous Sclerosing Cholangitis in *Mdr2*^{-/-} Mouse



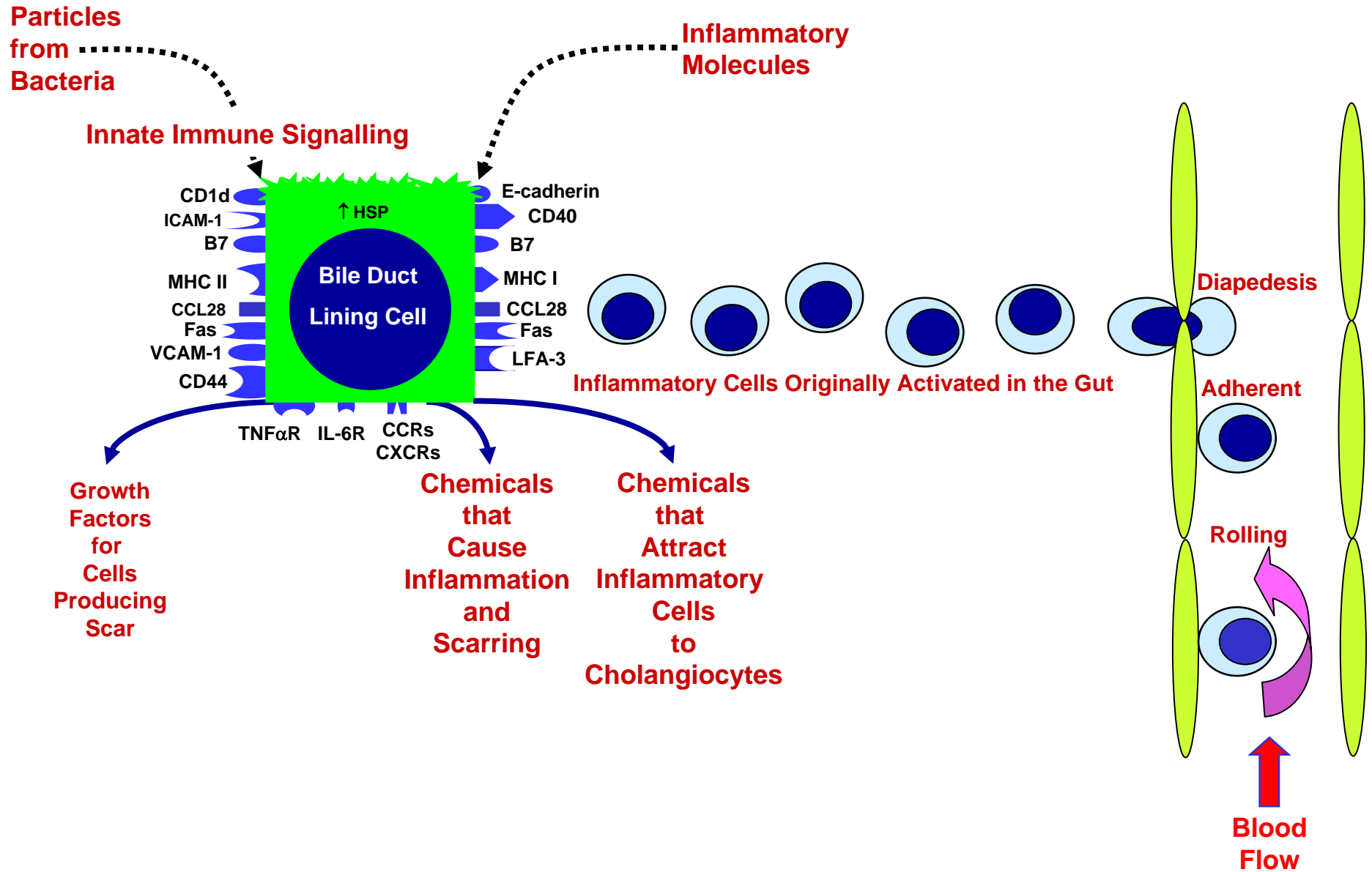
Immune Mechanisms in Sclerosing Cholangitis

Spontaneous Sclerosing Cholangitis in *Mdr2*^{-/-} Mouse

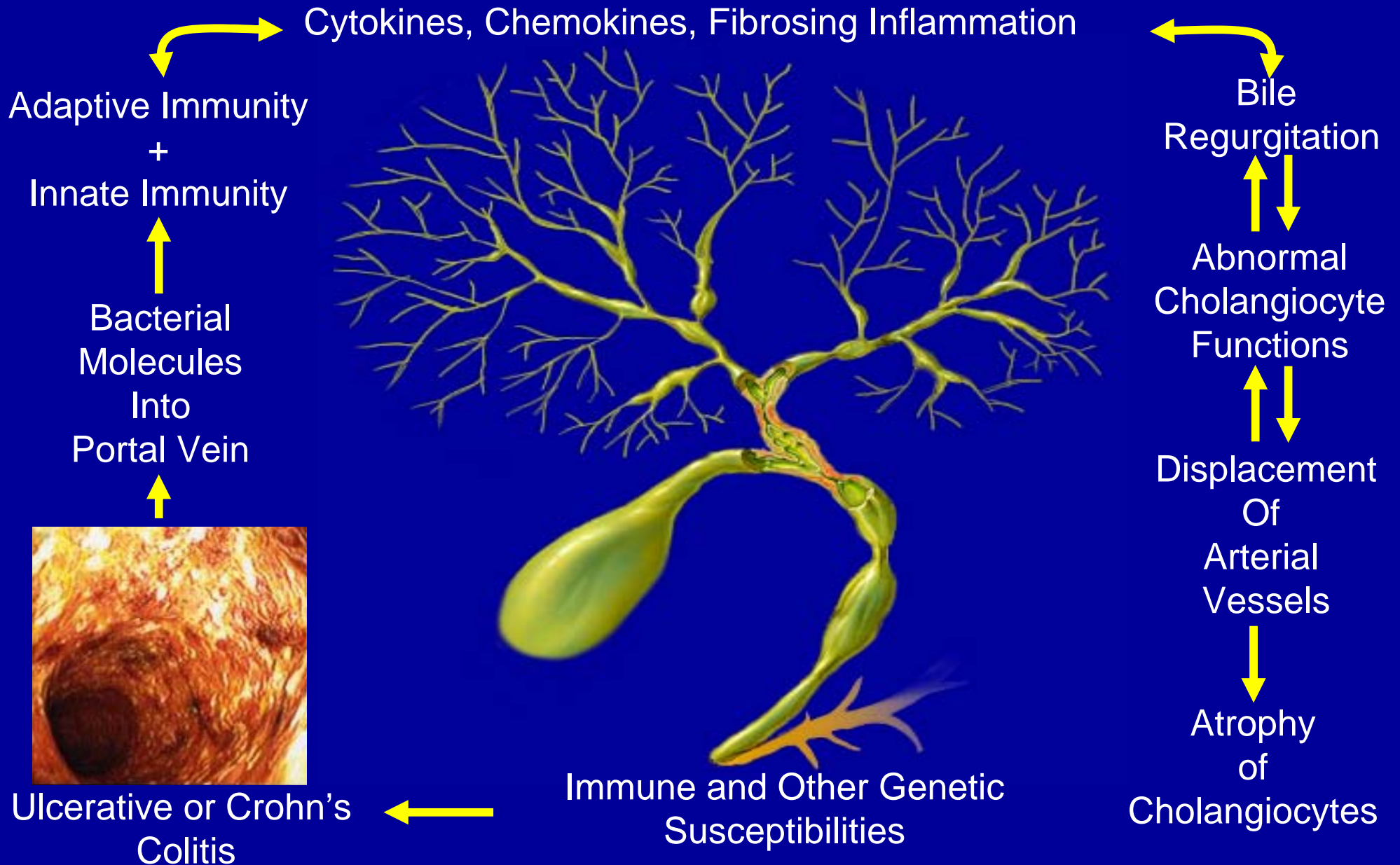
- Genetic cause of bile leak between bile duct lining cells
- Bile triggers innate immune inflammation and adaptive immunity
- Innate immune cells produce inflammatory chemicals
- These chemicals activate cells to form scar around the bile duct
- As the scar thickens, blood vessels pushed away from the bile duct
- Shrinkage of the lining cells of the bile duct due to lack of oxygen and nutrition supplied by



Immune Reactions in PSC



Possible Sequence of Events in Primary Sclerosing Cholangitis



Immunology of Primary Sclerosing Cholangitis

- Fund research!
- Without your advocacy, we will remain, in the words of Pogo:

“Surrounded by insurmountable opportunities.”