

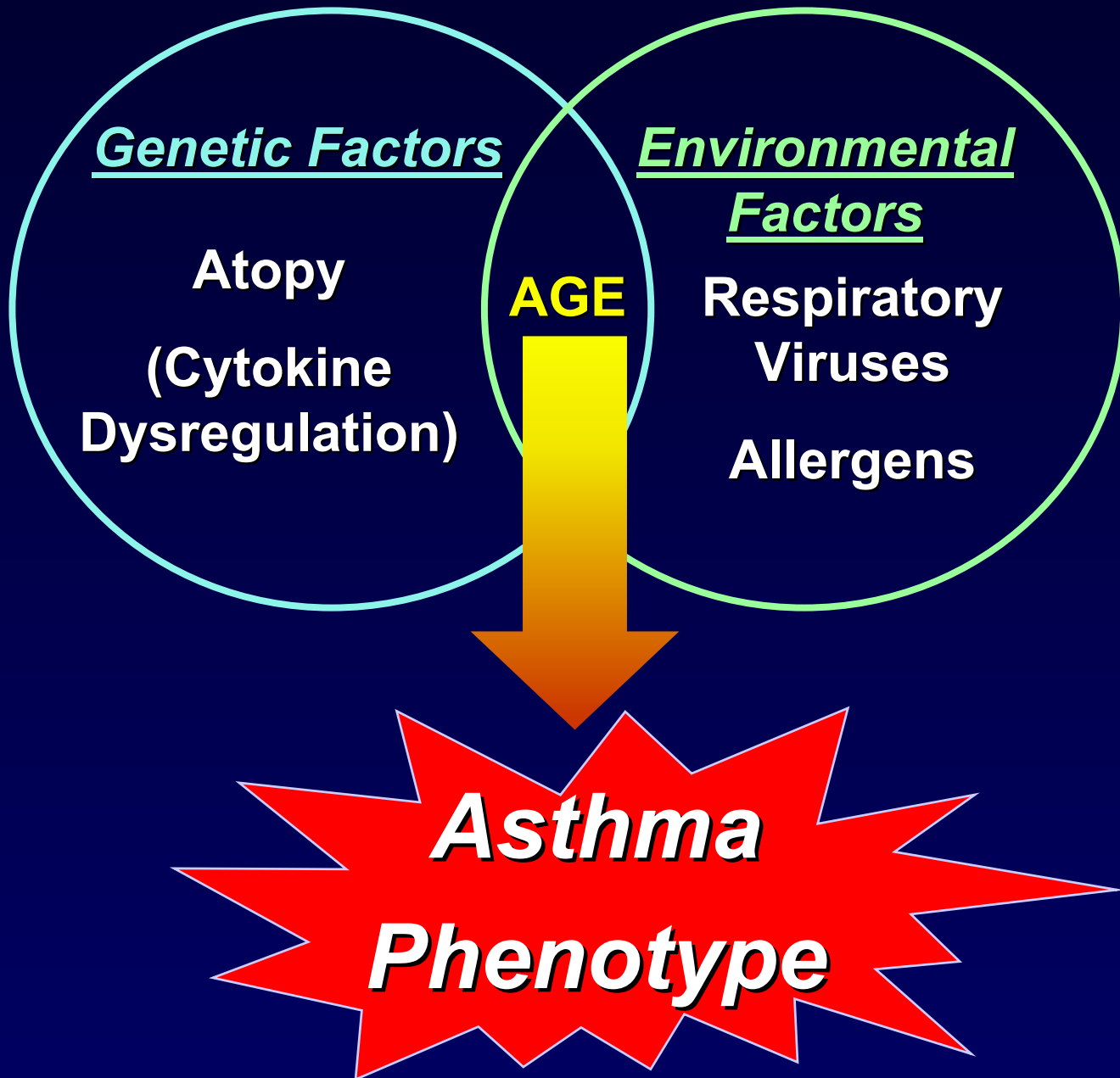
Asthmatic Phenotypes in the PhysGen Consomic Rats

UW-MCW Collaboration: Project Update

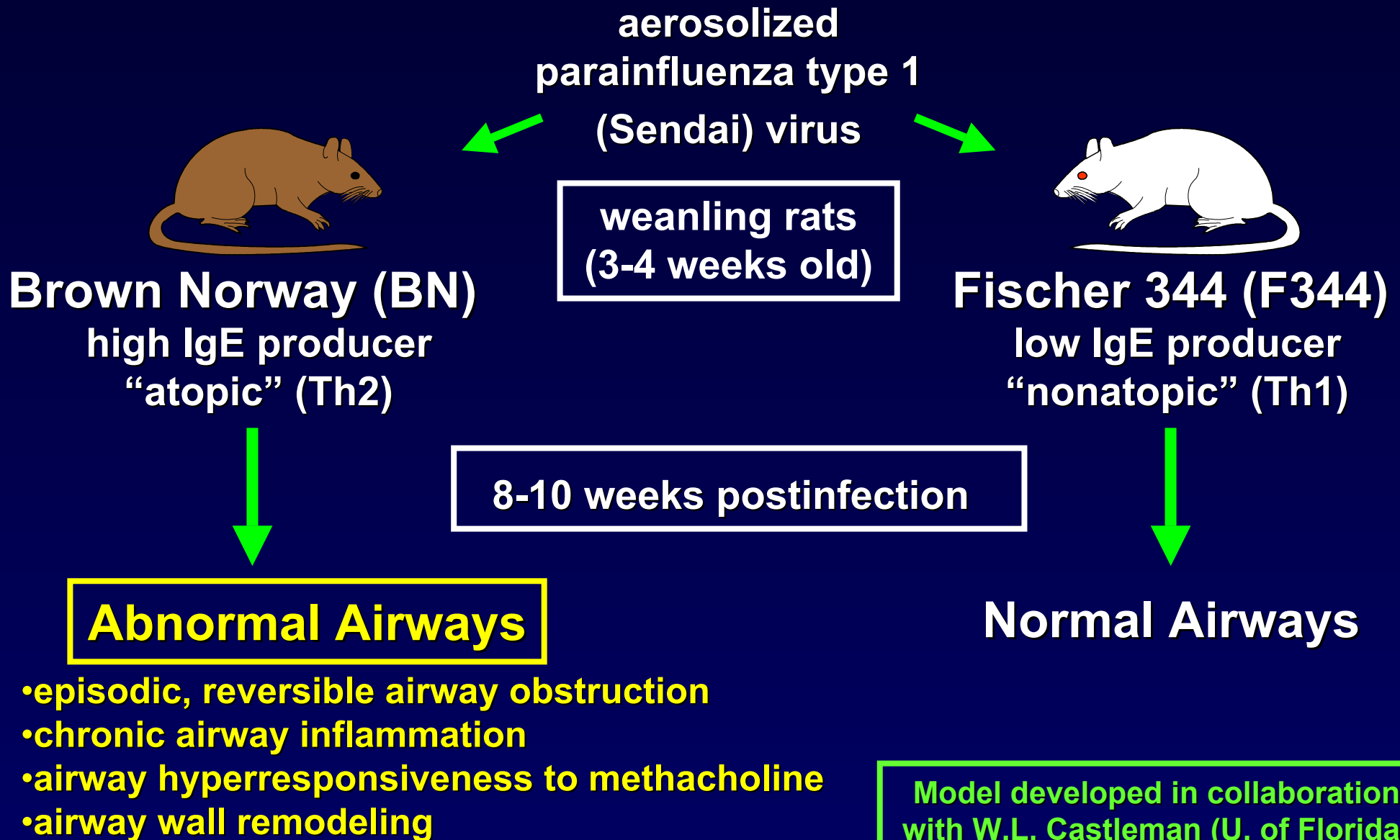
L.A. Rosenthal, R.L. Sorkness, and R.F. Lemanske, Jr.

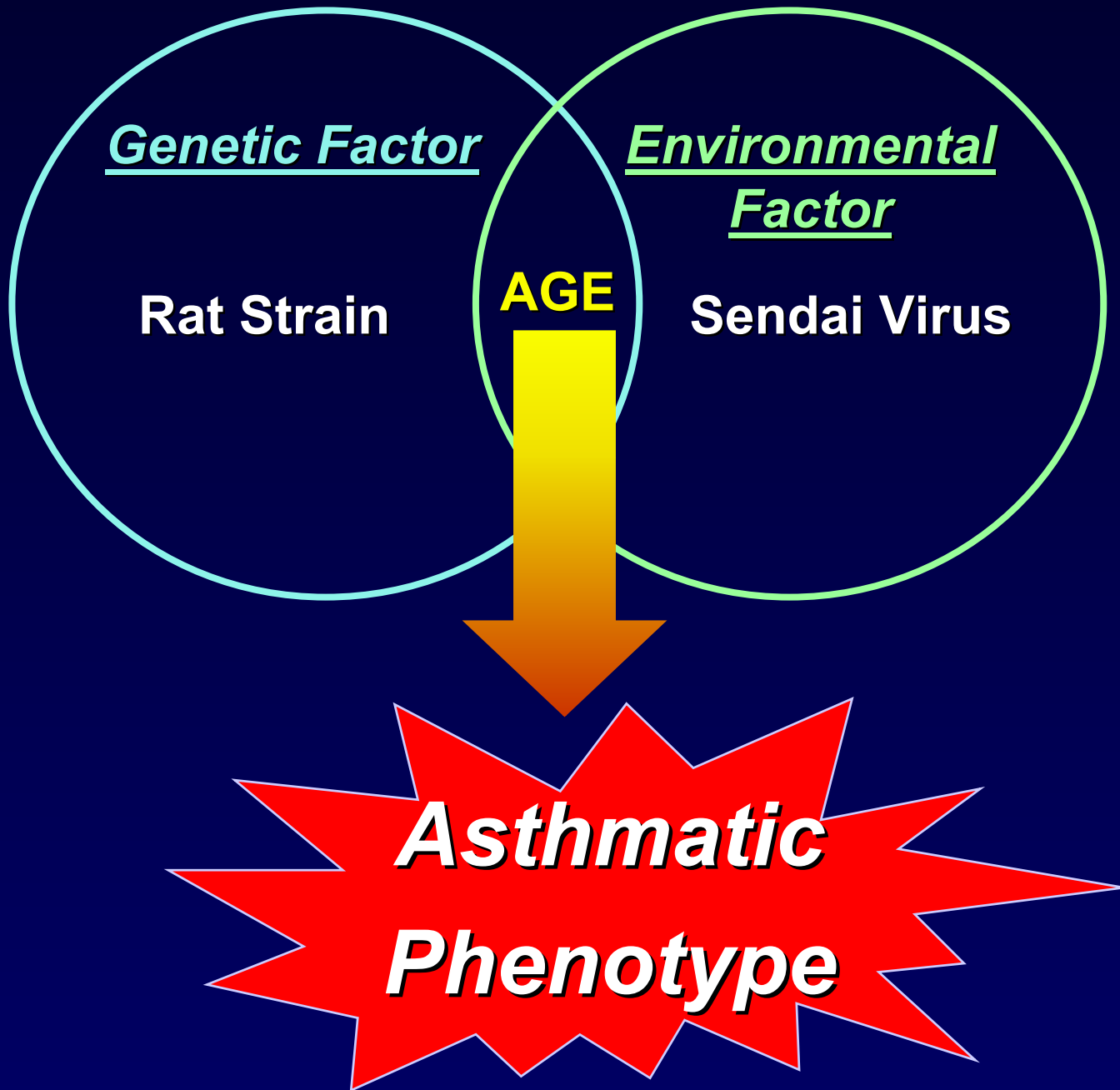
Morris Institute for Respiratory Research





Post-bronchiolitis Asthma-like Phenotype





Development of the Post-bronchiolitis Asthma-like Phenotype in Brown Norway Rats:

Host Response (*Genetic Factor*)

to Sendai Virus (*Environmental Factor*)

During Early Life (*Developmental Factor*)

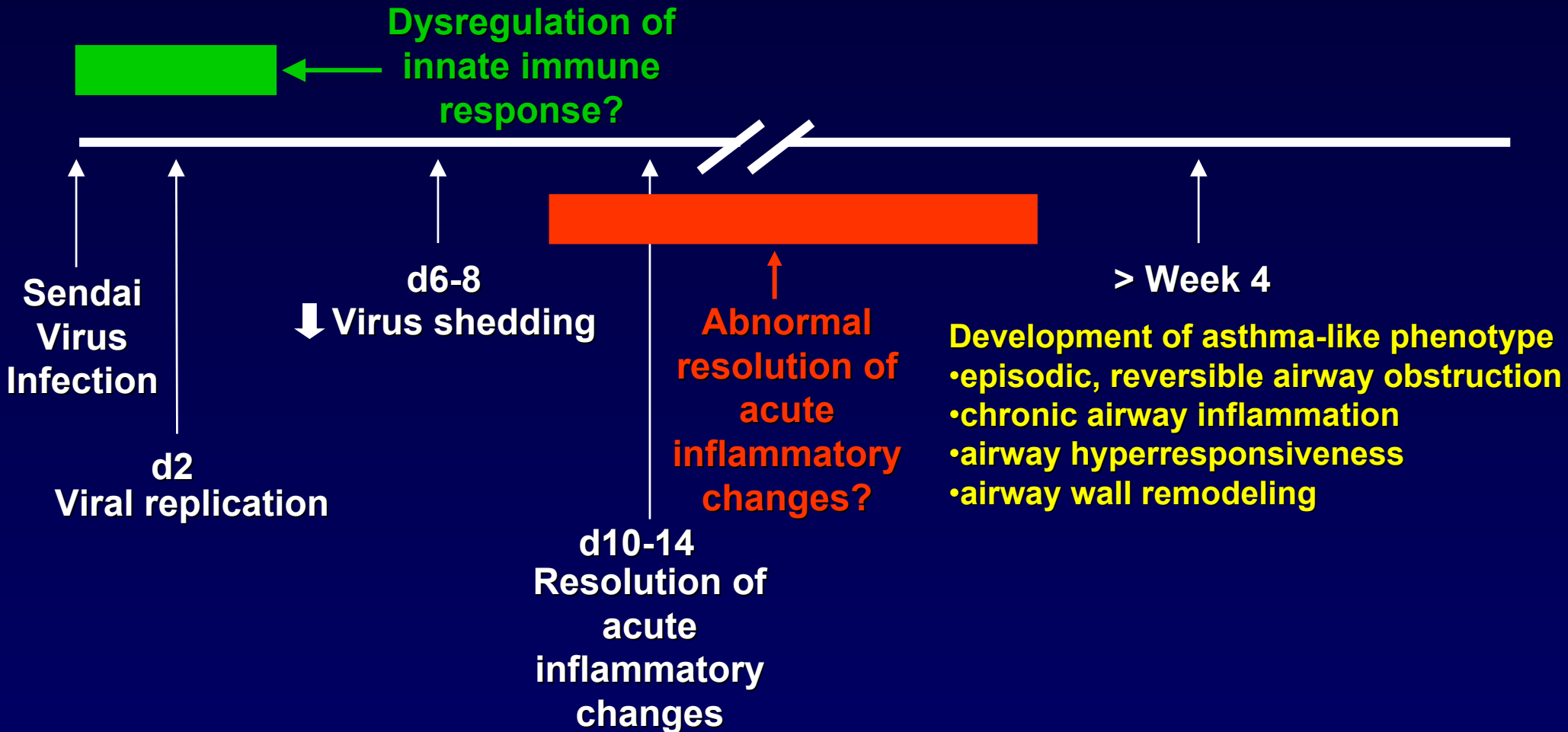
Drives Process

Acute Phase

**BN and F344:
Bronchiolitis**

Chronic Phase

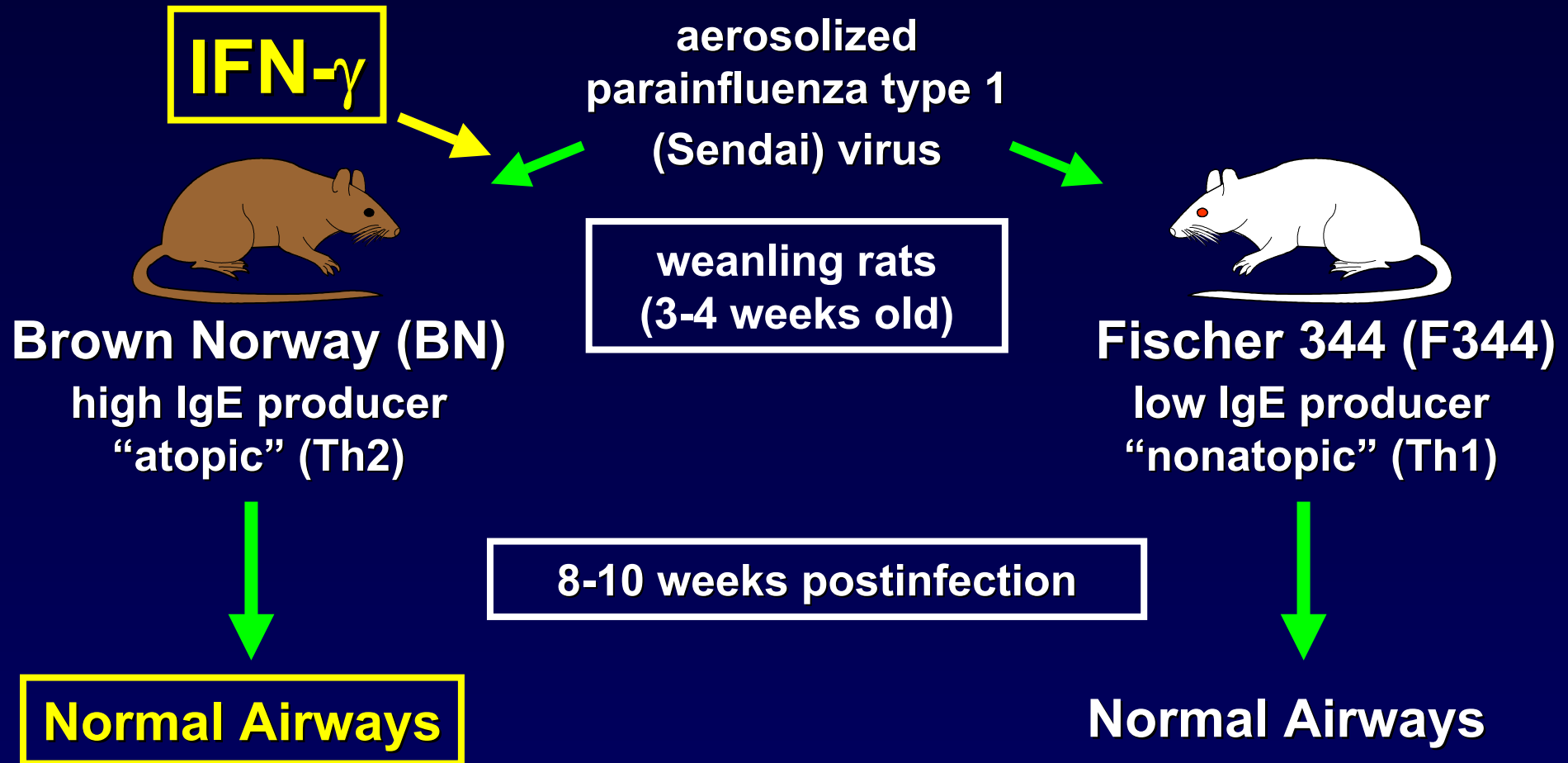
**BN: YES
F344: NO**



Development of Asthma-like Phenotype: Importance of IFN- γ During Acute Phase

- **IFN- γ in bronchoalveolar lavage fluid during acute Sendai virus infection in weanling rats:
F344 > BN**
- **Aerosolized IFN- γ prevents the development of post-bronchiolitis chronic airway dysfunction in BN rats.**

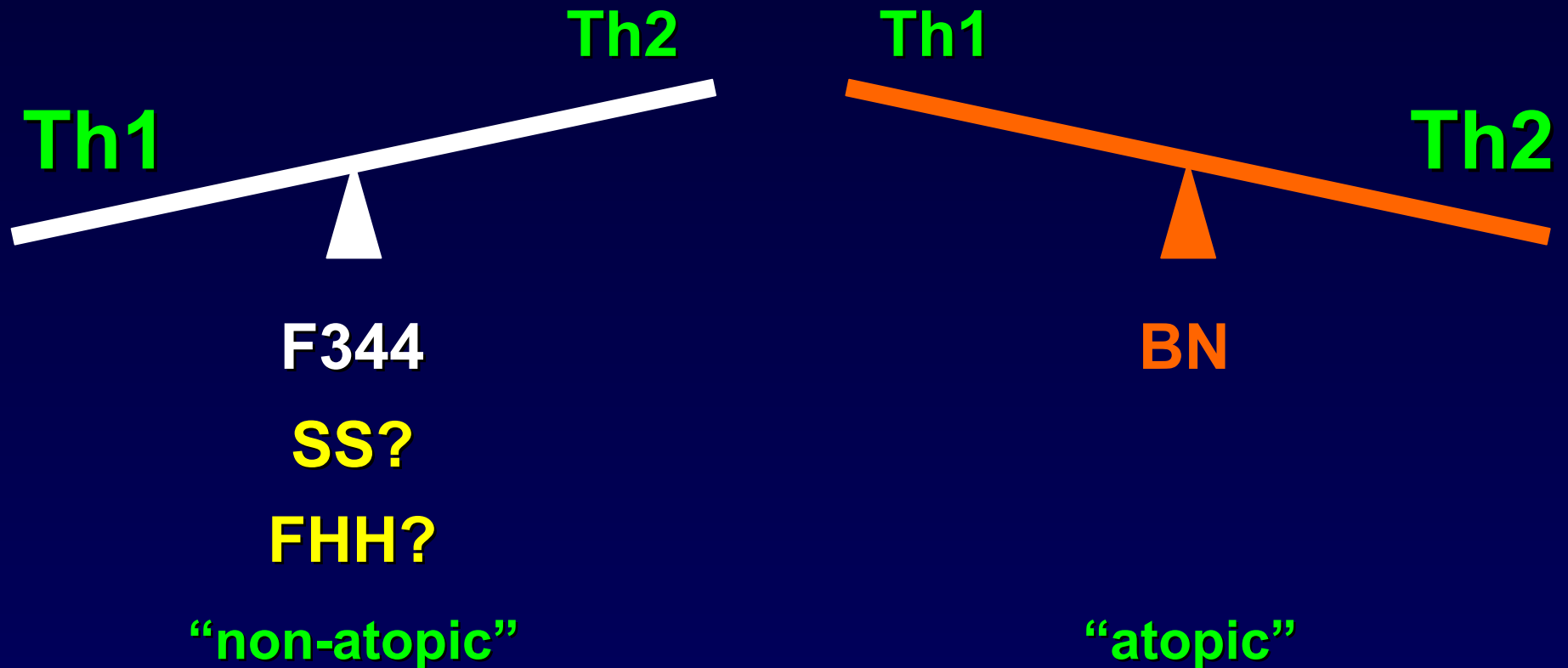
Post-bronchiolitis Asthma-like Phenotype



PhysGen Consomic Rats

- Parental strains for consomic rats:
 - Dahl salt sensitive (SS; hypertension model)
 - Fawn hooded hypertensive (FHH; hypertension and end-stage renal disease model)
 - **Brown Norway (BN; control strain: normotensive)**
- Useful for studying the role of genetic factors in susceptibility/resistance to the development of the post-bronchiolitis asthma-like phenotype?

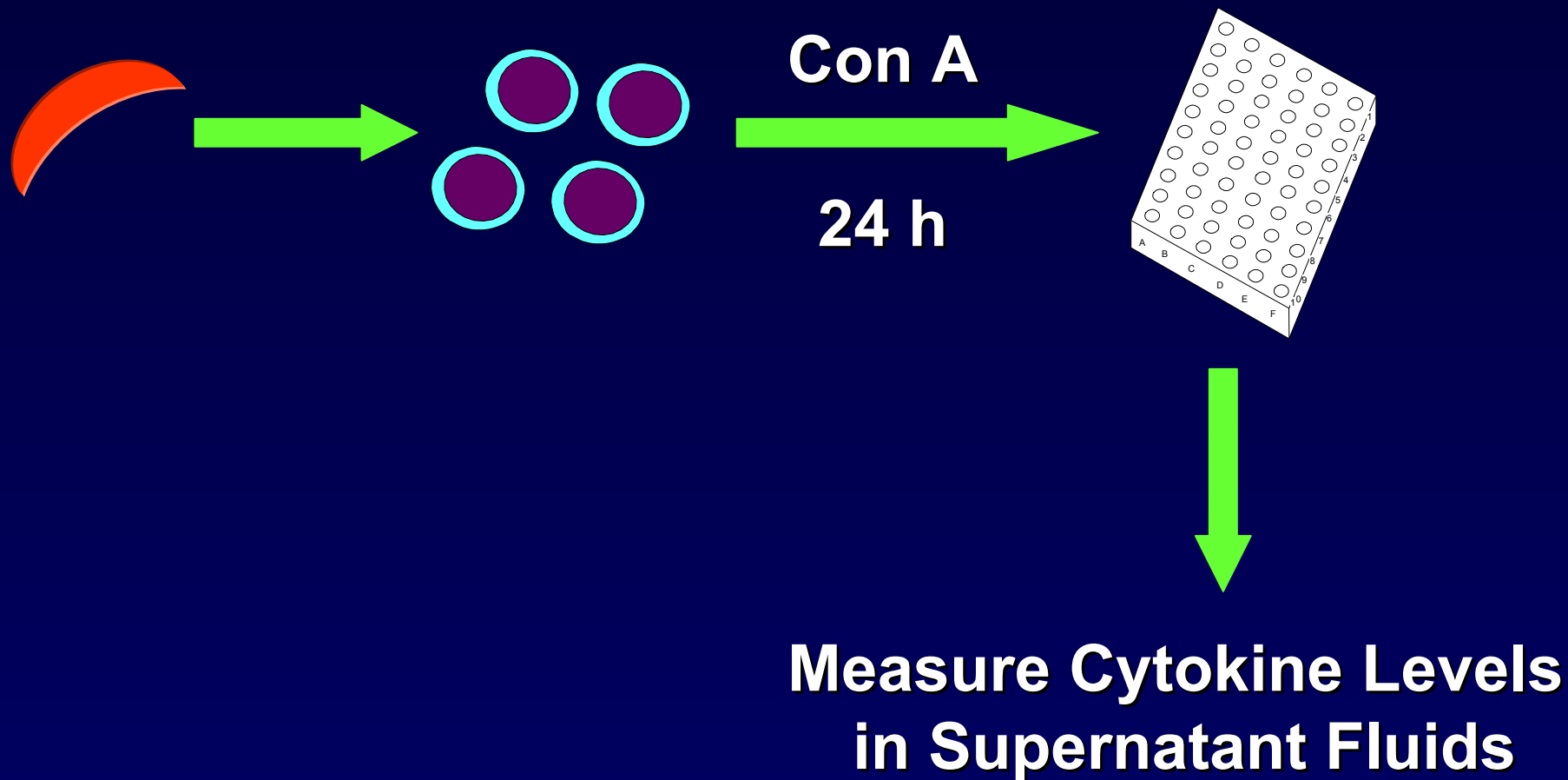
Balance Between Th1- and Th2-type Cytokines



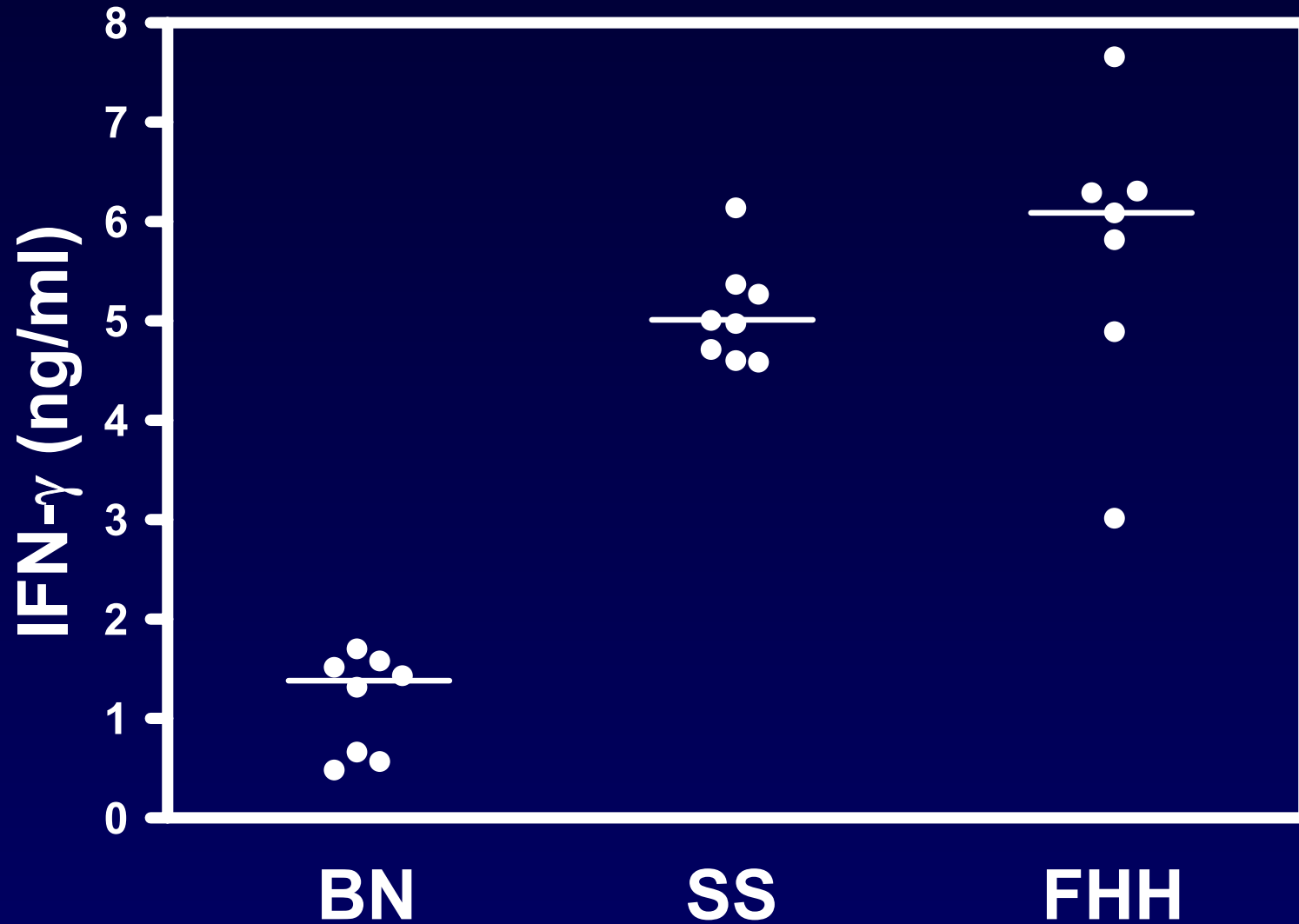
Th1-type: IFN- γ , IL-12; Th2-type: IL-4, IL-5, IL-13

**Are the Immune Responses of SS and FHH
Rats Th1-biased Like Those of F344 Rats?**

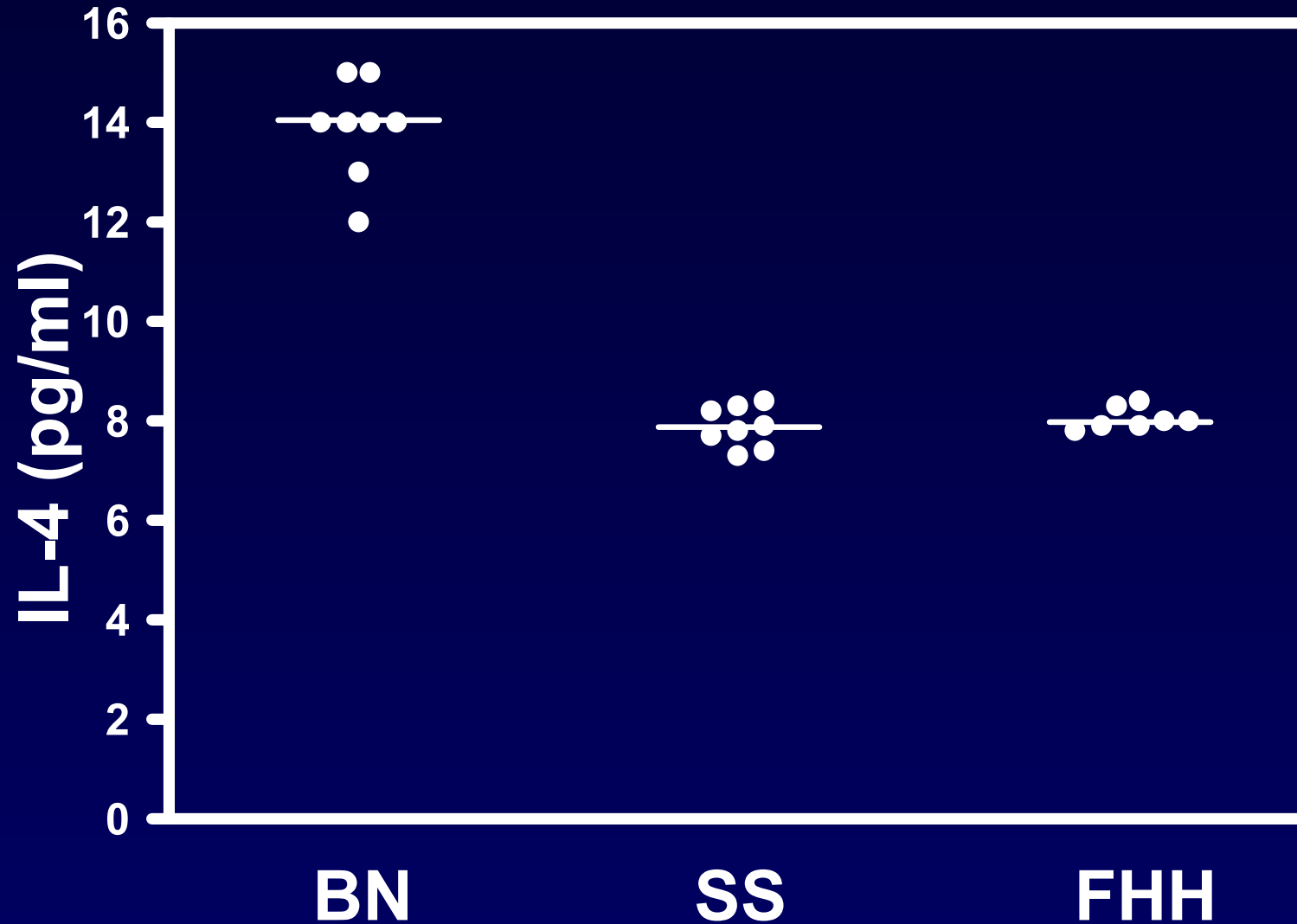
Screening Assay for Th1- and Th2-type Cytokine Production by Spleen Cells



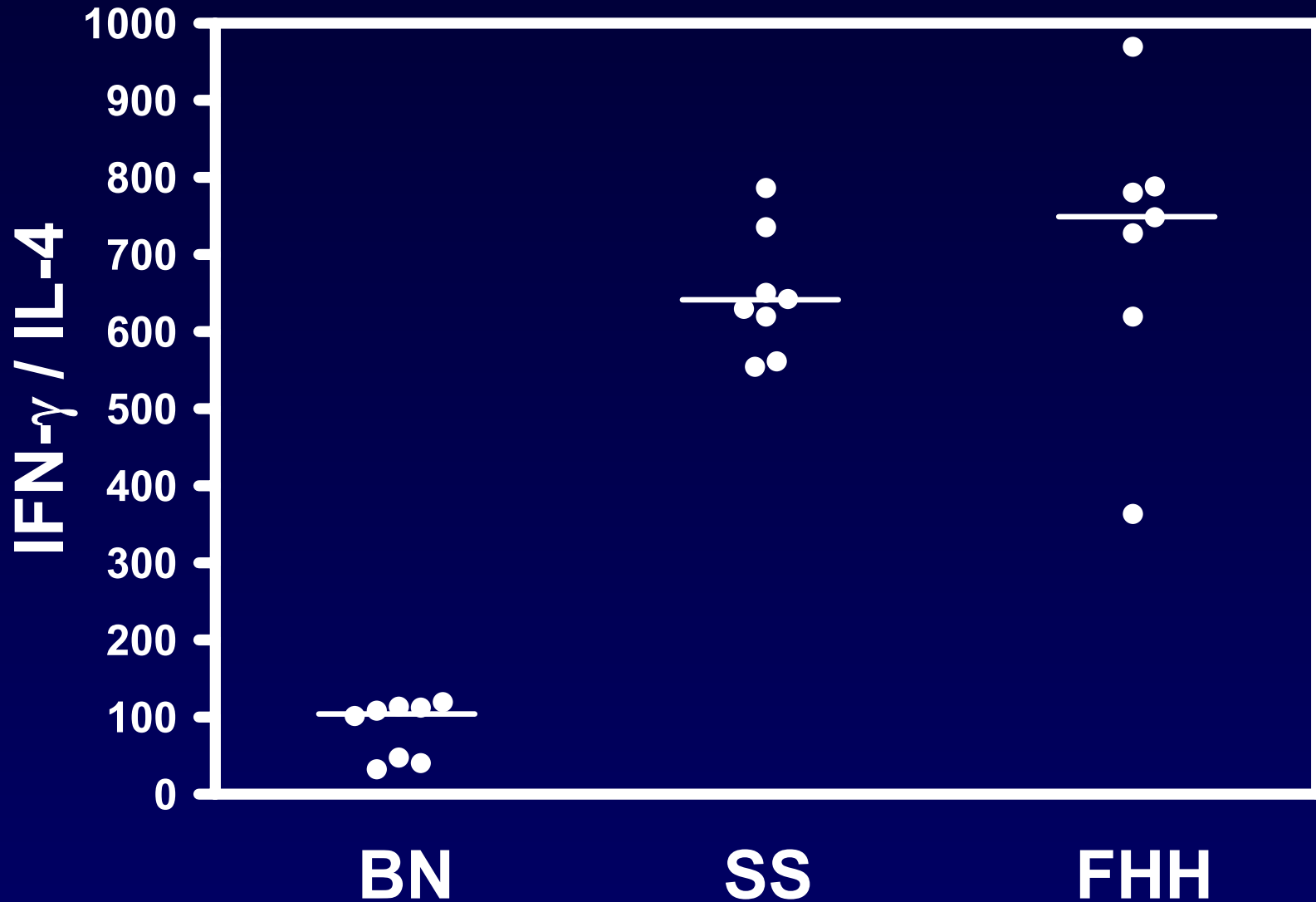
IFN- γ Production by Con A-stimulated Spleen Cells



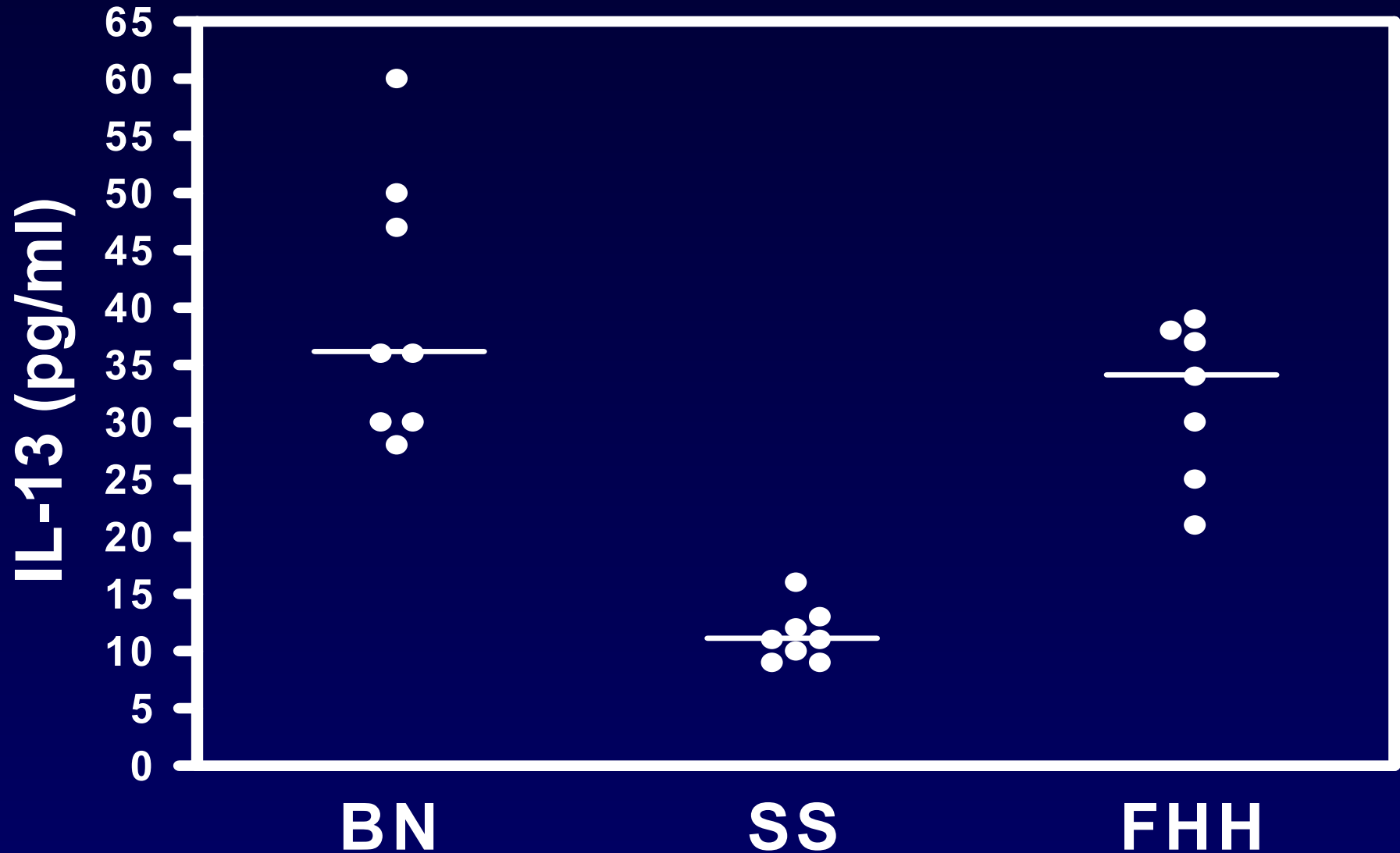
IL-4 Production by Con A-stimulated Spleen Cells



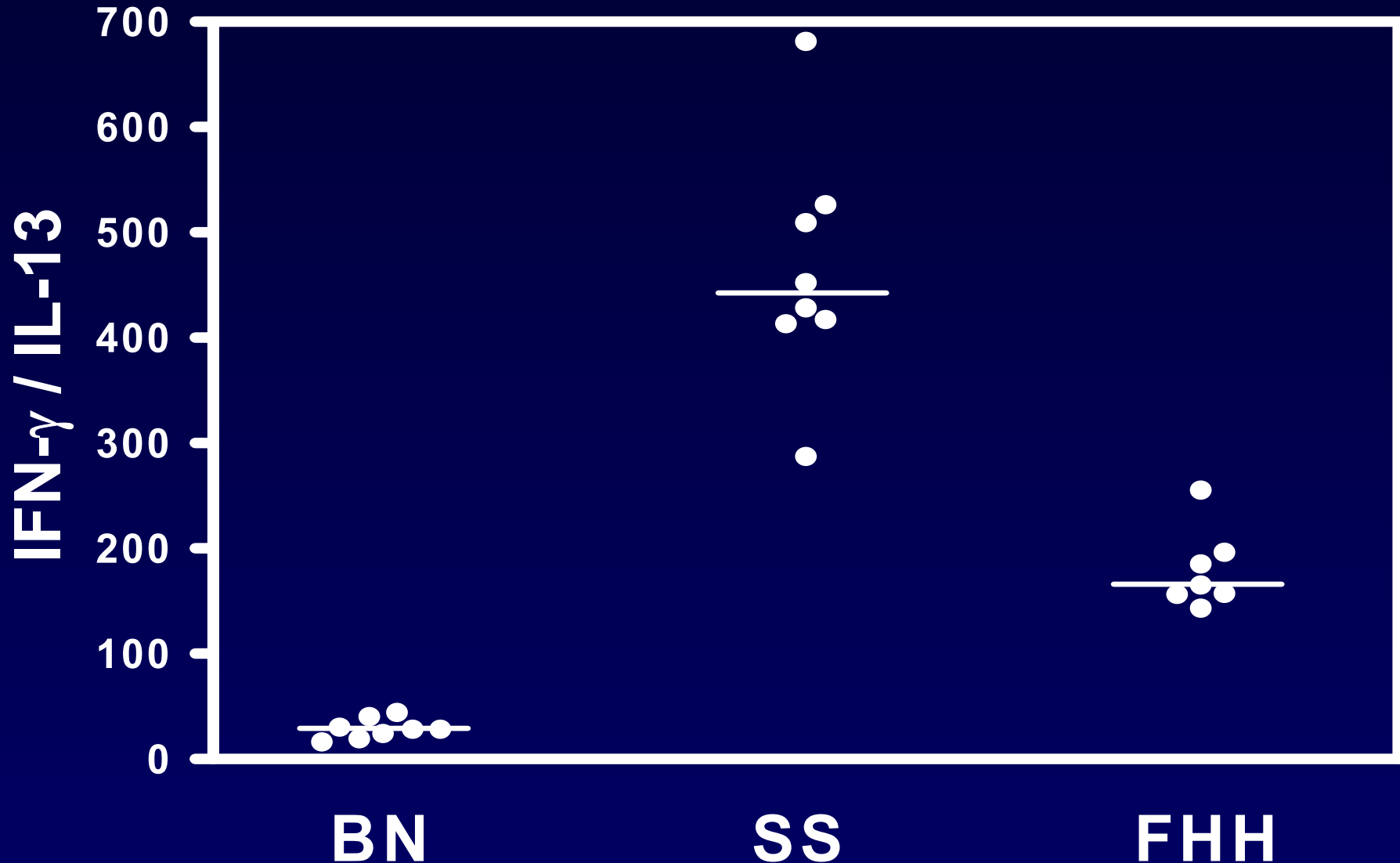
IFN- γ /IL-4 Ratio for Con A-stimulated Spleen Cells



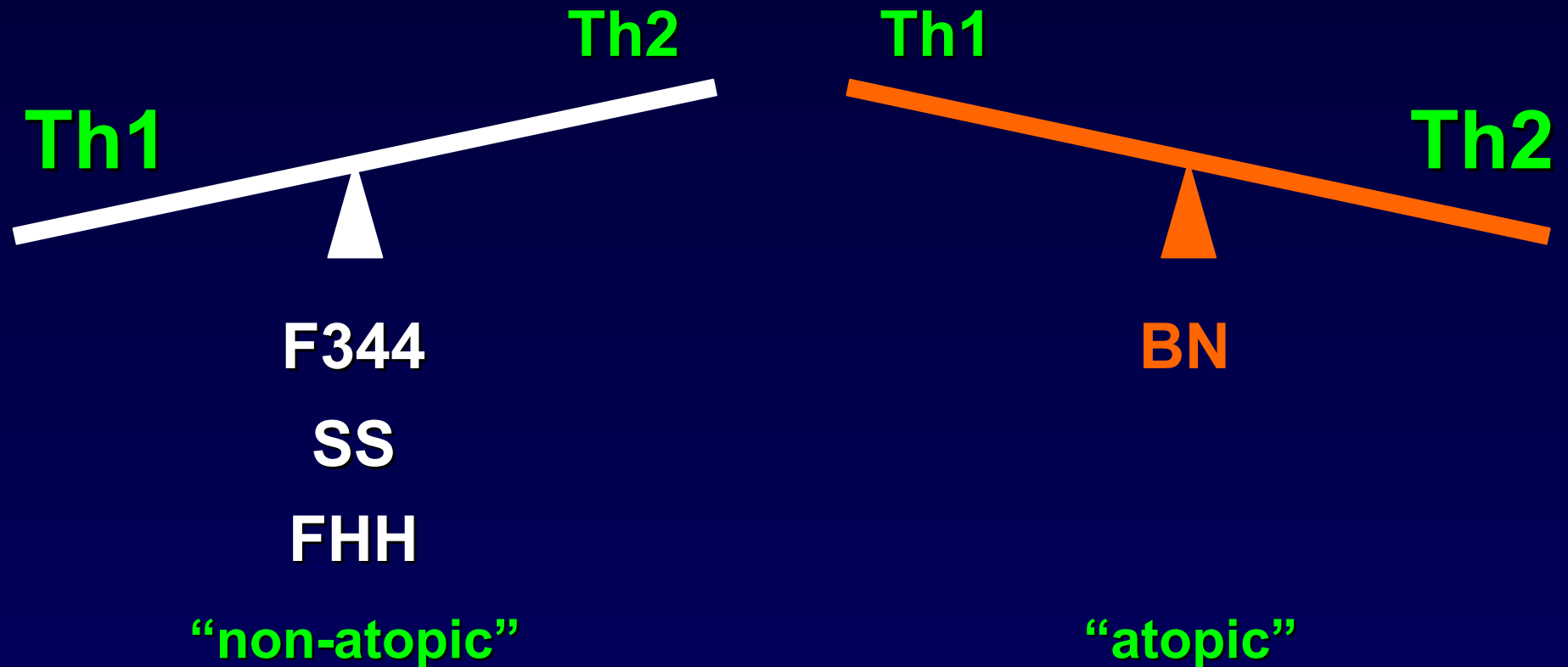
IL-13 Production by Con A-stimulated Spleen Cells



IFN- γ /IL-13 Ratio for Con A-stimulated Spleen Cells



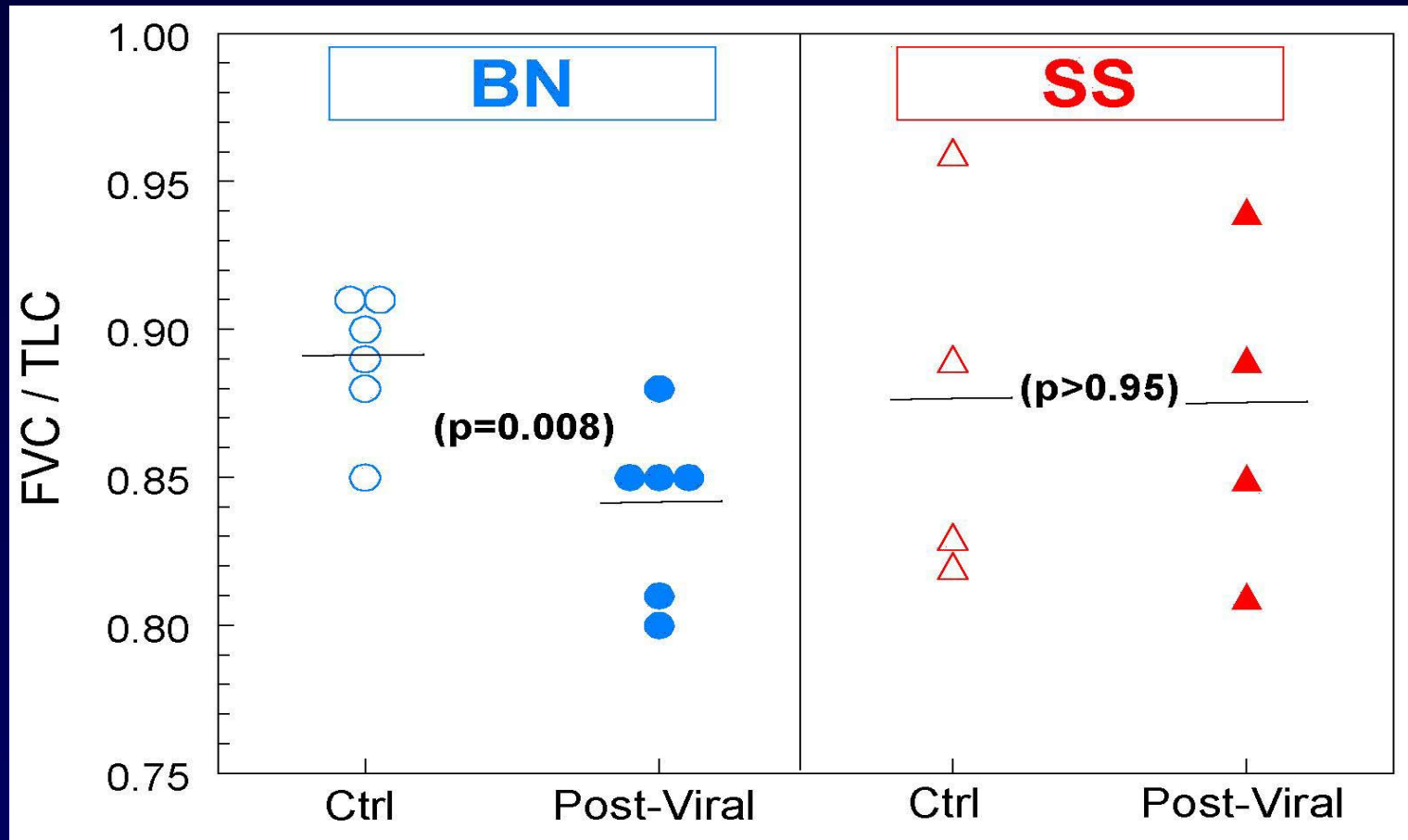
Balance Between Th1- and Th2-type Cytokines



Th1-type: IFN- γ , IL-12; Th2-type: IL-4, IL-5, IL-13

**Are SS Rats, Like F344 Rats, Resistant to the
Development of Post-bronchiolitis Airway
Dysfunction?**

Post-bronchiolitis Airway Dysfunction in BN, but not SS, Rats

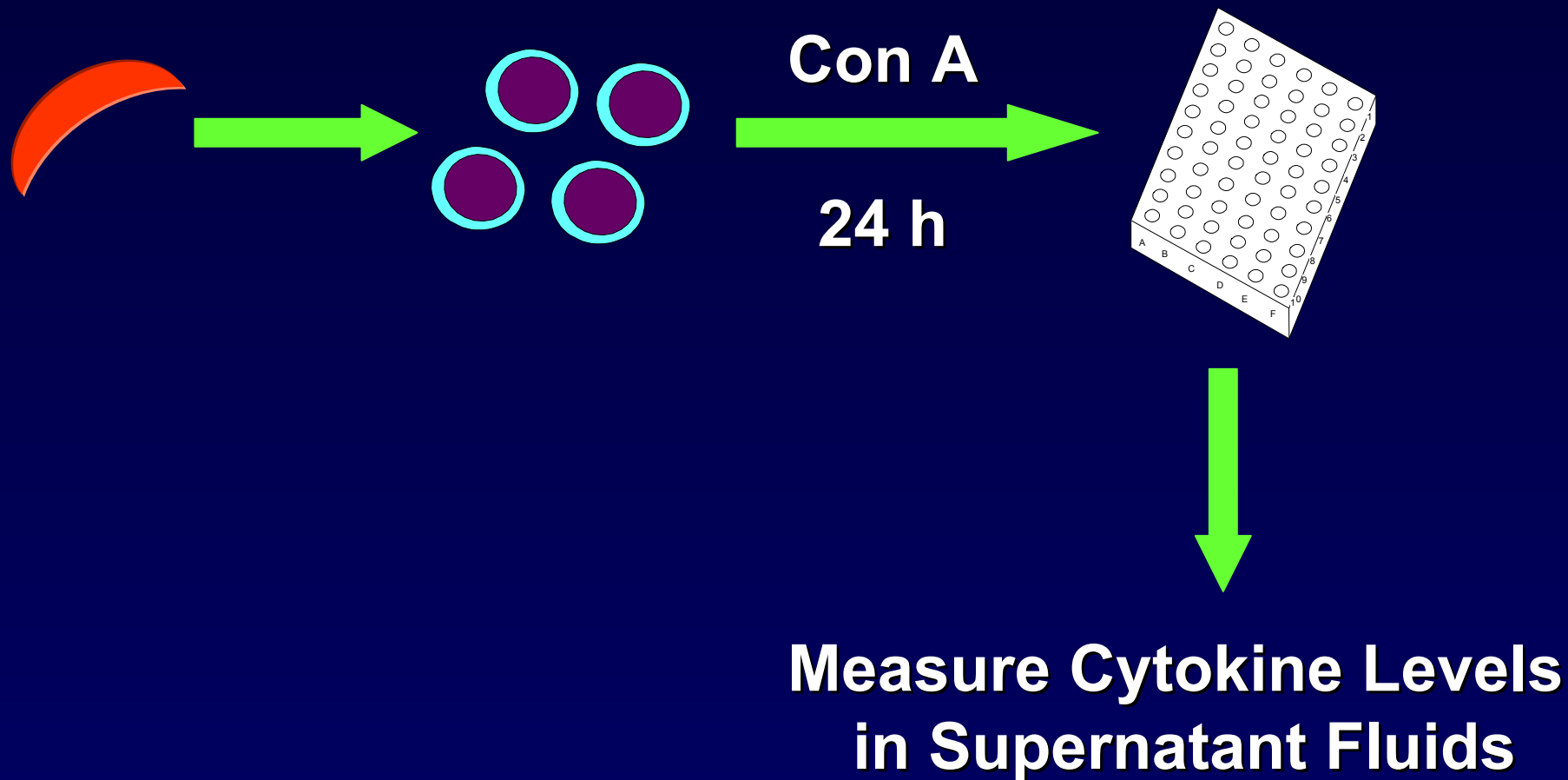


Therefore, *in vitro* cytokine data and *in vivo* physiology data suggest that the PhysGen consomic rat strains will be useful tools for studying the role of genetic factors in susceptibility/resistance to the development of the post-bronchiolitis asthma-like phenotype.

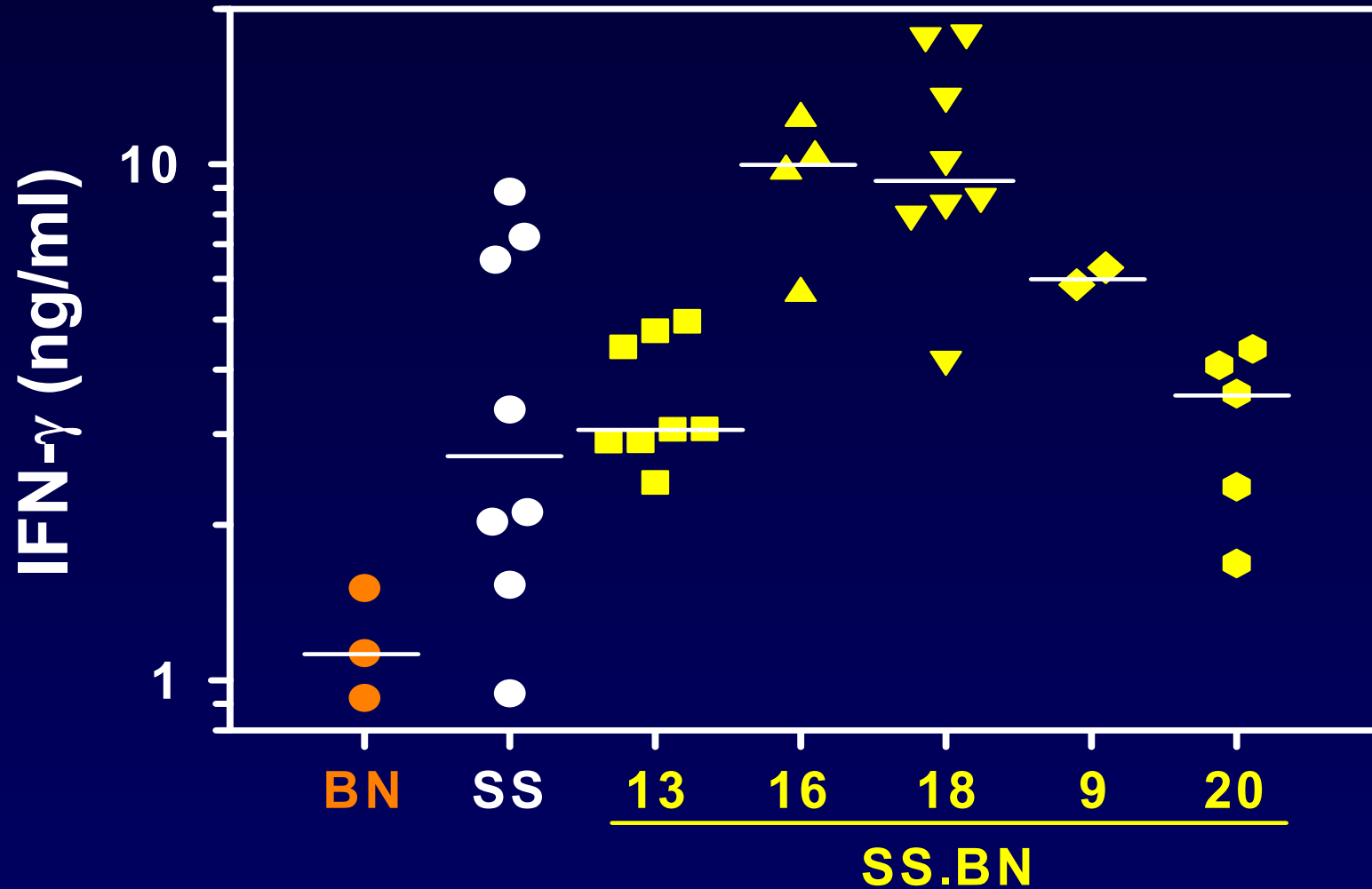
Screening of Consomic Rat Strains

- **SS.BN13**
- **SS.BN16**
- **SS.BN18**
- **SS.BN9**
- **SS.BN20**

Screening Assay for Th1- and Th2-type Cytokine Production by Spleen Cells



IFN- γ Production by Con A-stimulated Spleen Cells



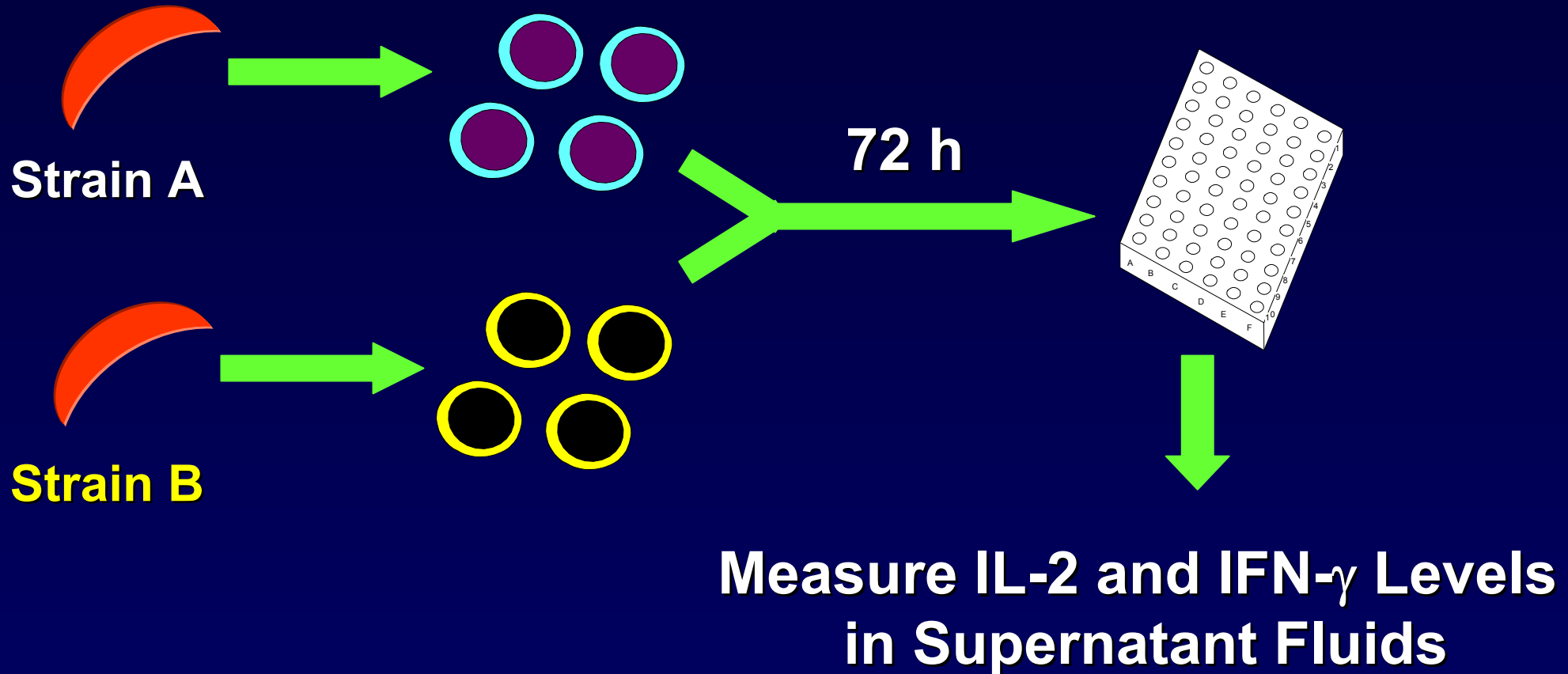
Th1 and Th2 Cytokine Production

- **No strain differences were observed among SS and these five SS.BN strains with regard to Con A-stimulated IFN- γ production [or IL-4 or IL-13 production (not shown)] .**

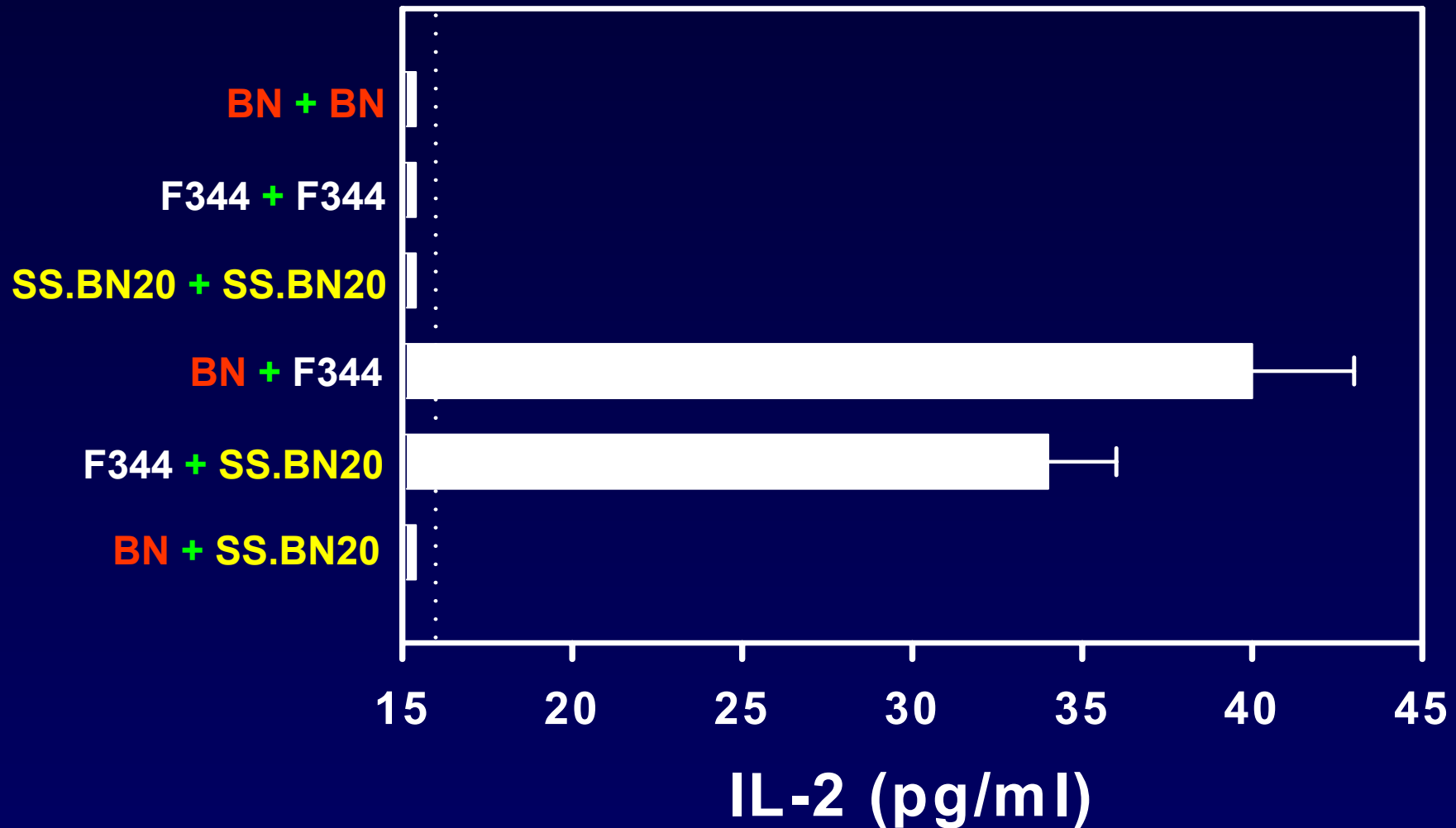
Chr. 20: Major Histocompatibility Complex

- **SS.BN20**
 - **Histocompatible with BN?**
 - **Histoincompatible with SS?**

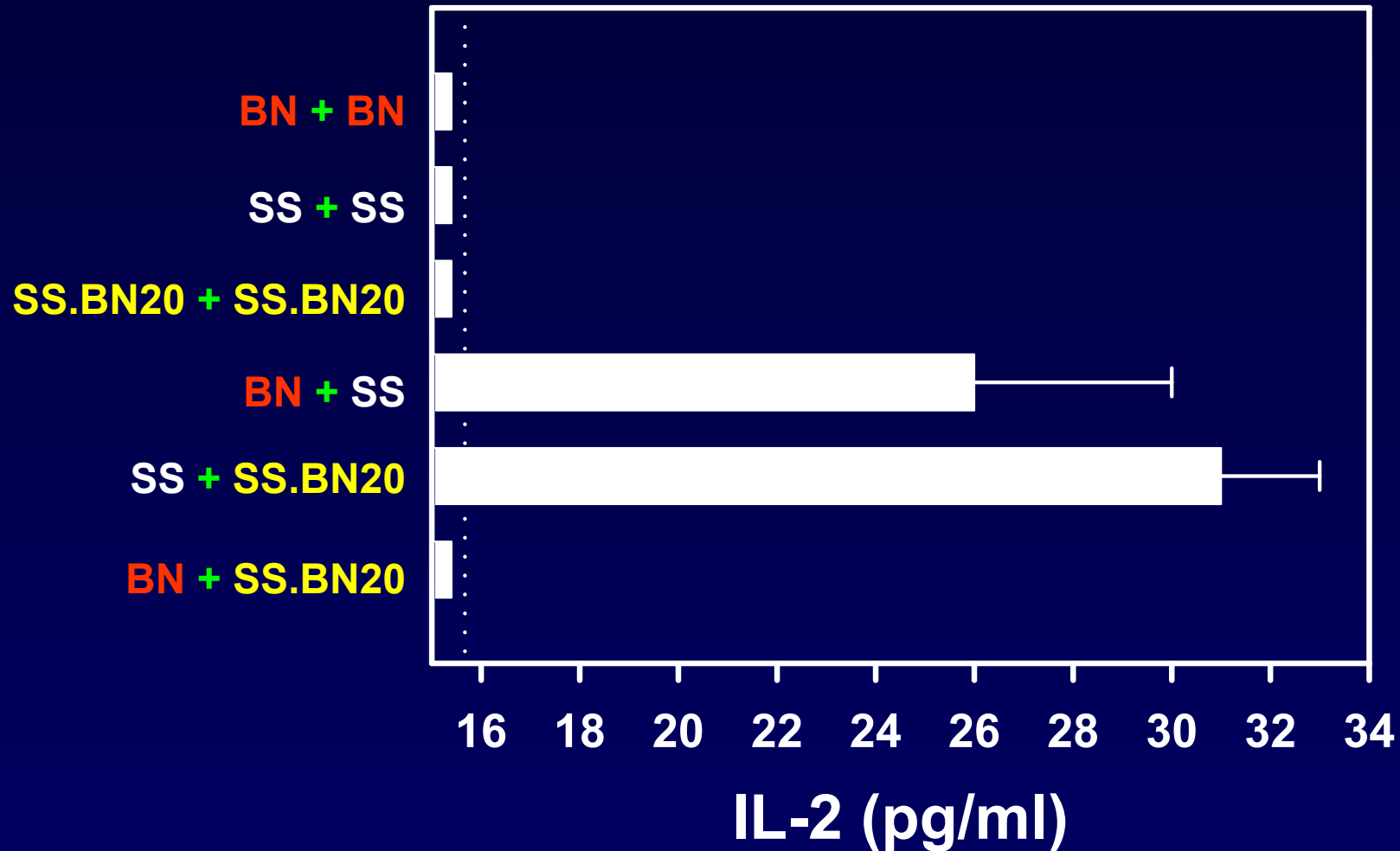
Two-way Mixed Lymphocyte Cultures



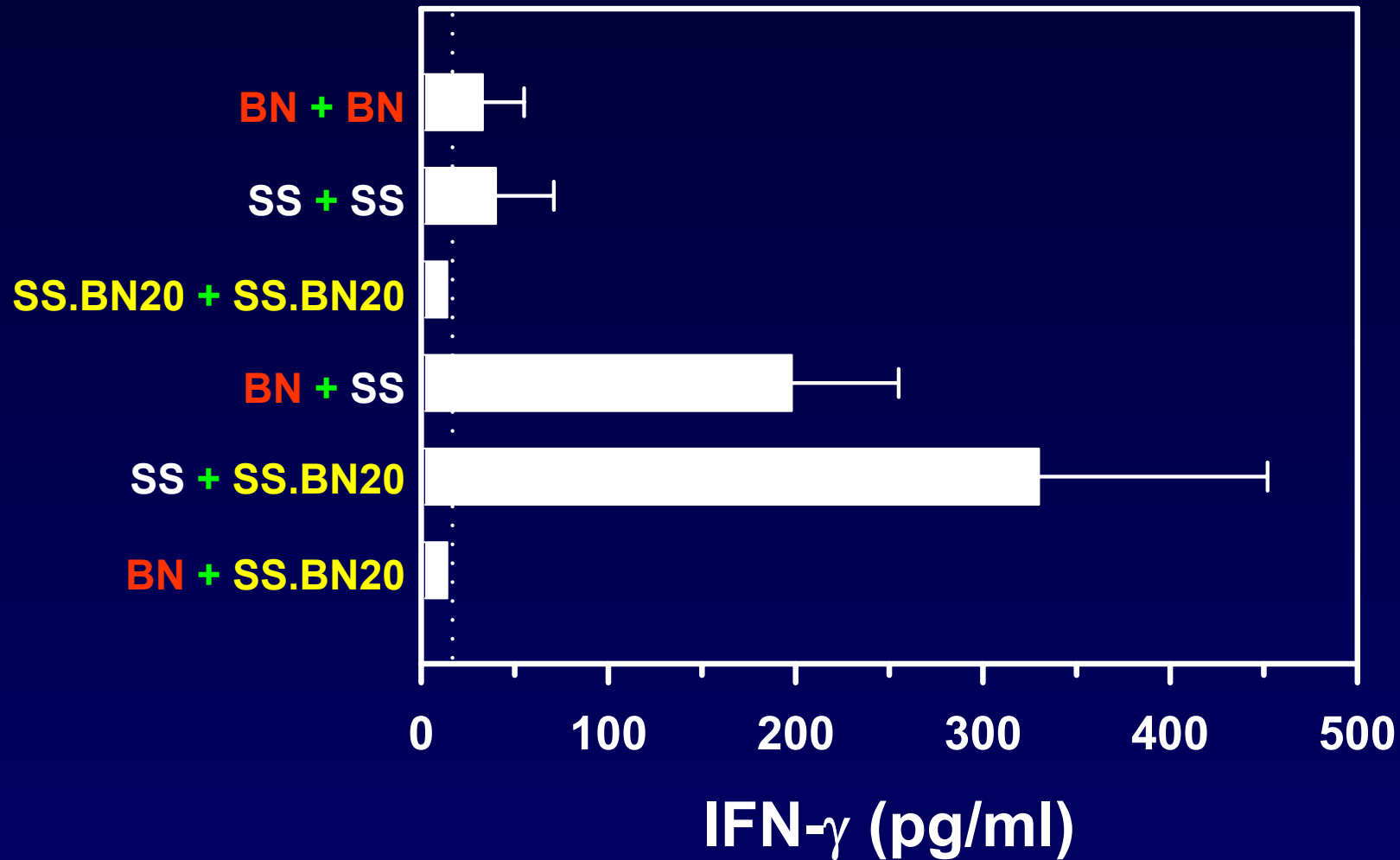
IL-2 Production in 2-way Mixed Lymphocyte Cultures: BN and SS.BN20 Splenocytes are Histocompatible



IL-2 Production in 2-way Mixed Lymphocyte Cultures: SS and SS.BN20 Splenocytes are **Histoincompatible**



IFN- γ Production in 2-way Mixed Lymphocyte Cultures: SS and SS.BN20 Splenocytes are Histoincompatible



Potential Uses of the Histocompatible SS.BN20 Strain for Studies in BN Rats

- **in vitro**
 - **cell mixing studies**
- **in vivo**
 - **adoptive cell transfer studies**
 - **organ transplant studies**

PhysGen Consomic Rat Development Timeline

- SS.BN12
- FHH.BN1 (IL-4R α)
- SS.BN6 (Immunoglobulin)
- SS.BN7 (IFN- γ)
- SS.BN8
- Fischer CDF(F-344)CrIBR
- BN/SsNHsd/Mcw

<http://pga.mcw.edu>

Future Directions

- **Continue screening spleens from adult consomic rats.**
- **PhysGen consomic rat strains to be distributed through Charles River Laboratories.**
- **Availability of weanling consomic rats will significantly increase options with regard to screening.**
- **Level of characterization of weanlings from each consomic strain? Resources that will inform these decisions include:**
 - **Rat Genome Database; Rat Genome Sequencing Project**
 - **Virtual Comparative Maps**
 - **MCW-TIGR microarray expression profiling of rat consomic panels (lung)**

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