

Charles River Laboratories



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Major Points in selecting strains/stocks for bioassays

1. For comparability in a global research environment, it is important to choose stocks or strains which are widely used.
2. International consistency within a stock or strain is also important, i.e., the rat or mouse used in North America is the same as in Europe or Asia.
3. Outbred stocks are overwhelmingly selected, primarily Sprague-Dawley type rats and albino outbred mice.
4. Whether inbred or outbred, genetic management is critical, at least as much so as health management.



Comparability

1. For comparability in a global research environment, it is important to choose stocks or strains which are widely used.

- The existence of a substantial database of background information is an important consideration
- Find statements by ICH (CBC)
- Check EU goals on environmental chemicals (CBC)



Consistency

2. International consistency is also important, i.e., the rat or mouse in North America is the same as in Europe or Asia.
 - Requires actively managed program to insure consistency in health, genetics and environment



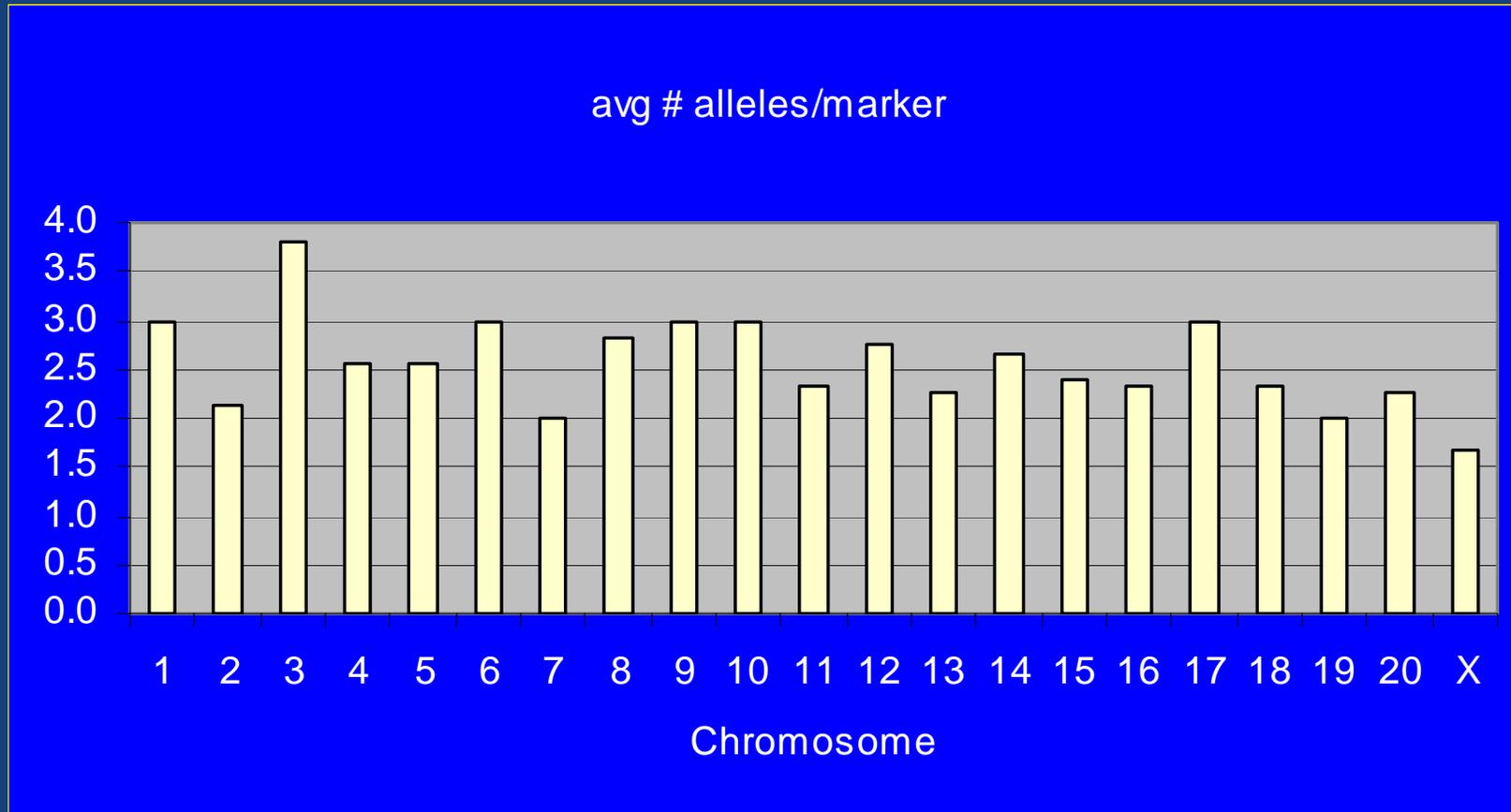
Inbred vs. Outbred

3. Outbred stocks are overwhelmingly selected, primarily Sprague-Dawley type rats and albino outbred mice.

- >75% mice and rats produced commercially in the US are non-inbred. (WJ White, Microbial Status and Genetic Evaluation of Mice and Rats: Proceedings of the 1999 US/Japan Conference (2000), National Academy Press).
- Genetic variation, although limited, exceeds that of inbred or F1 hybrid stocks used for their uniformity.
- Proper genetic management maintains current heterogeneity.



CD microsatellite monitoring



Non-Inbred

(e.g., random bred or outbred)

- Animals derived from mating unrelated individuals
 - Desirable because of their increased individual genetic diversity, relative to inbred or F1 hybrid stocks.
 - Need to avoid inbreeding at all costs
 - Absolute genetic heterogeneity is never achieved
 - Selection pressure  Increased genetic drift



Random Bred (non-inbred)

- Assumes an unlimited population size
 - Every available reproductively fit animal has an equal chance of participating in the breeding program (no selection criteria)
 - All mating is done completely at random
 - Probably does not exist even in wild populations



Outbred (non-inbred)

- A purposeful system of mating that attempts to maintain genetic diversity by:
 - Minimizing the chance of inbreeding
 - Ensuring that a large percentage of the available population can participate in the breeding system
 - Minimizing/eliminating selection criteria
 - Ensuring a purposeful mixing of the breeding population



Maintenance of strain(s)

4. Whether inbred or outbred, genetic management is critical, at least as much so as health management

- Genetic drift is inevitable in isolated breeding populations, inbred as well as outbred
- Requires actively managed program to insure consistency over time



International Genetic Standard (IGS)

- A globally integrated genetic management system using pedigreed gnotobiotic foundation colonies, a program of regular breed stock migration and, for outbreds, a production system that avoids inbreeding



Isolators

GFC

Gnotobiotic Foundation Colony
Pedigreed (B X S)

Barrier Rooms

PNC

Pedigreed Nucleus Colony
(B X S)

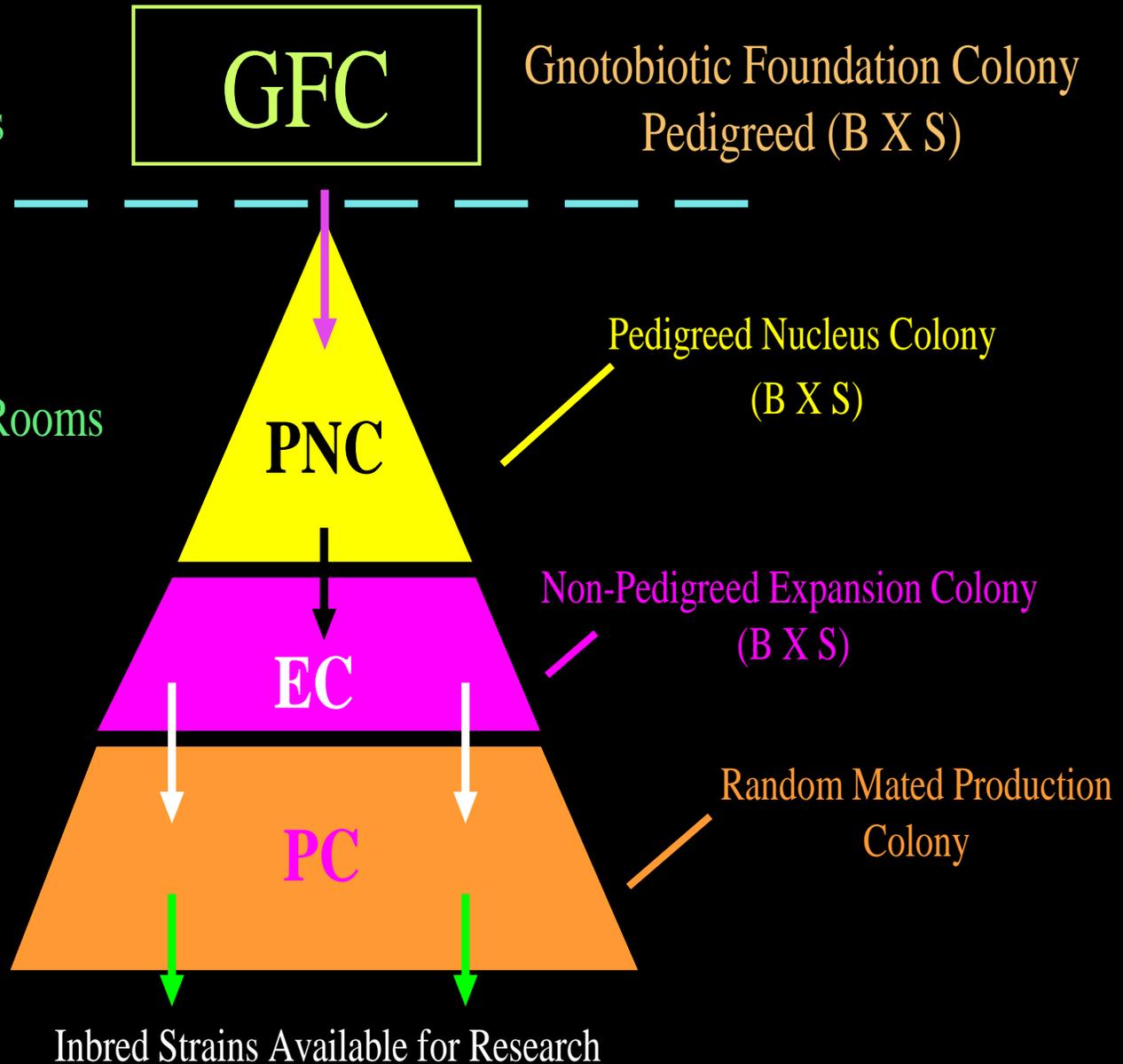
Non-Pedigreed Expansion Colony
(B X S)

EC

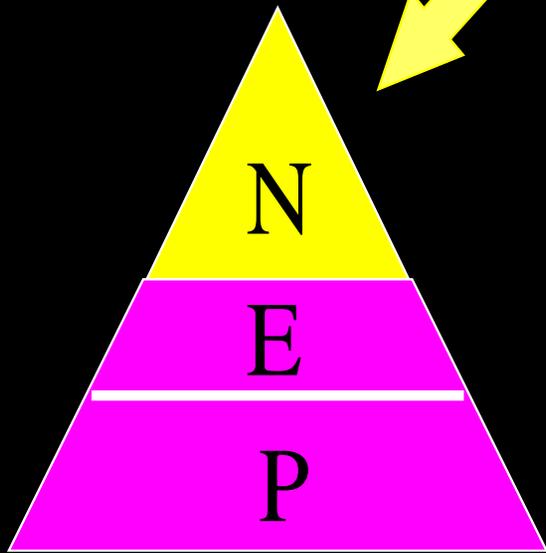
Random Mated Production
Colony

PC

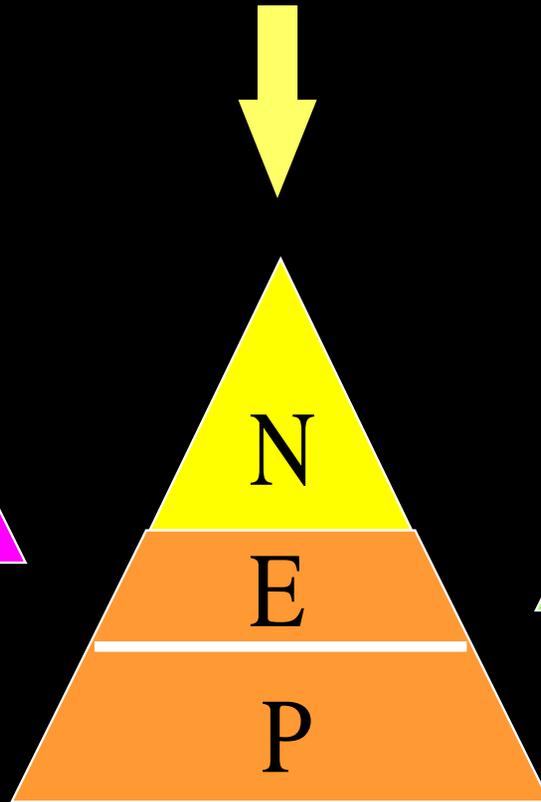
Inbred Strains Available for Research



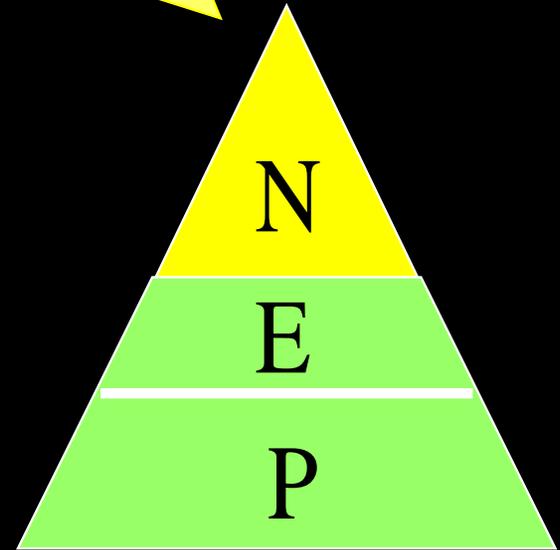
Corporate Inbred
Foundation Colony



Colony 1



Colony 2



Colony 3

Goal of Outbred Colony Management

- Maintain Heterozygosity
- Prevent temporal and spatial (geographic) genetic divergence of colony



What is basis of IGS system for CD rat?

- Captured the full scope of genetic diversity in the global CD rat population
- Links all CD rat populations making the degree of variation similar between colonies
- Minimizes selection pressures
- Standardizes a purposeful outbreeding system to maintain current level of genetic diversity



Outbred colony management

CD IGS Foundation Colony Production

Isolators



HM prior to Release

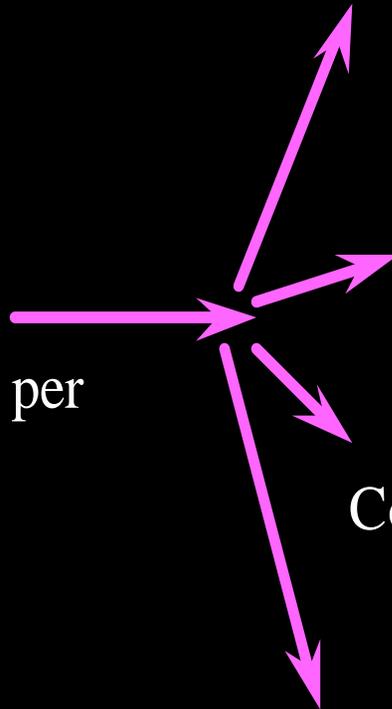
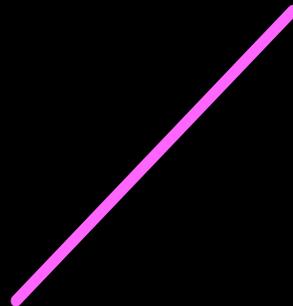
480
Weanlings per week

Foundation
Future Breed
Replacement

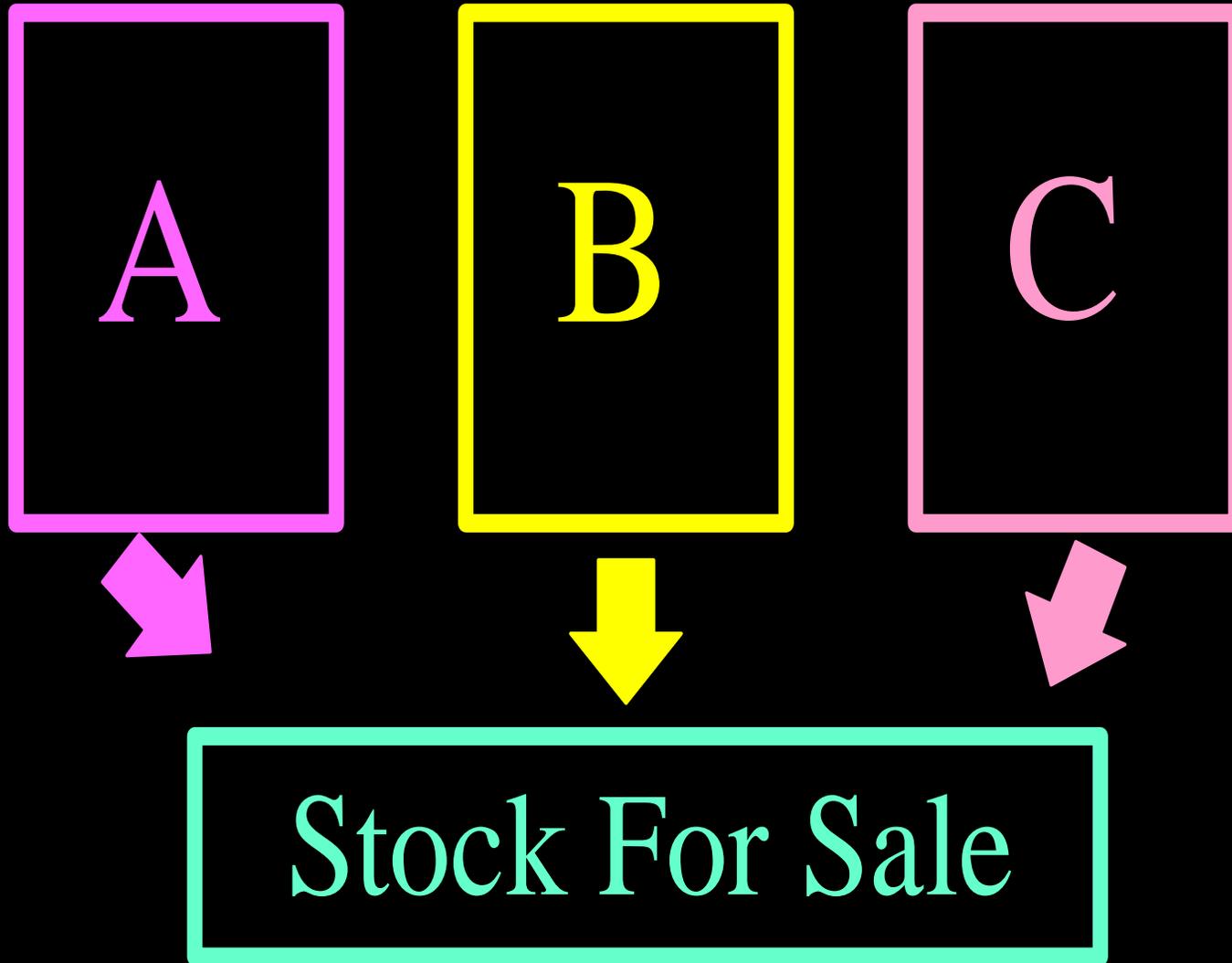
Forward
Migration

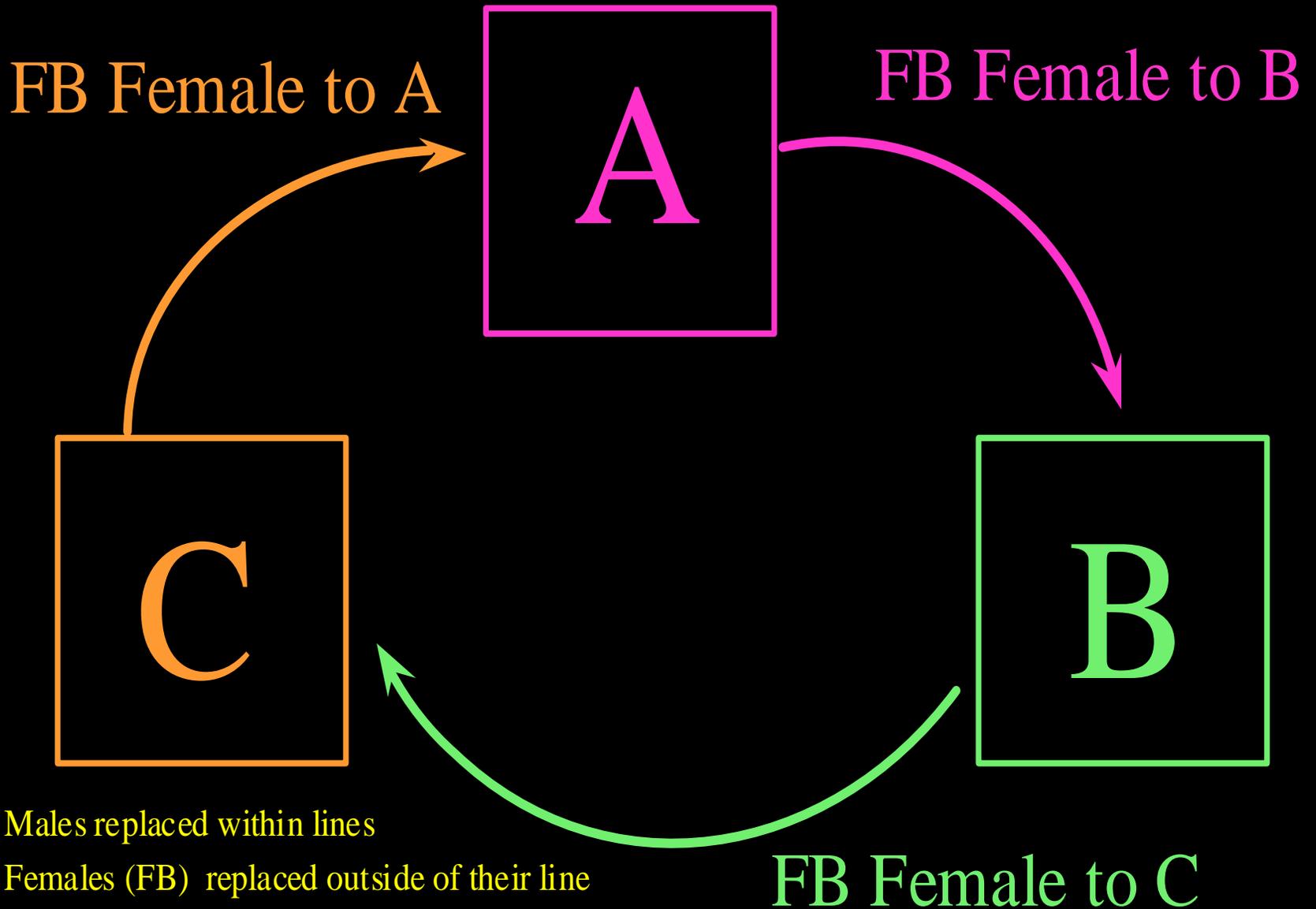
Colony Set up

Limited Sale of Over
Production

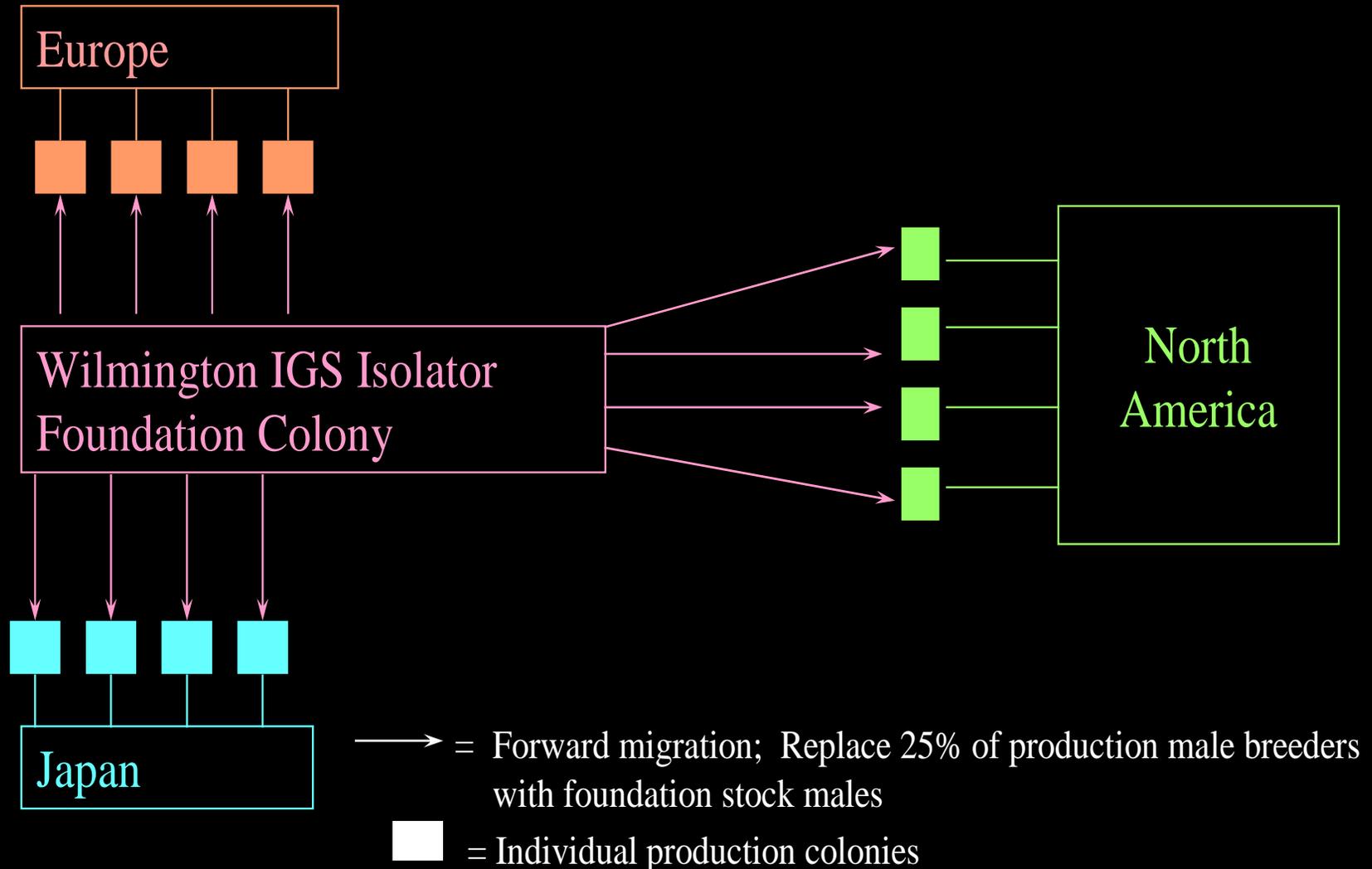


Outbred colony management
Polygamous Production Colony

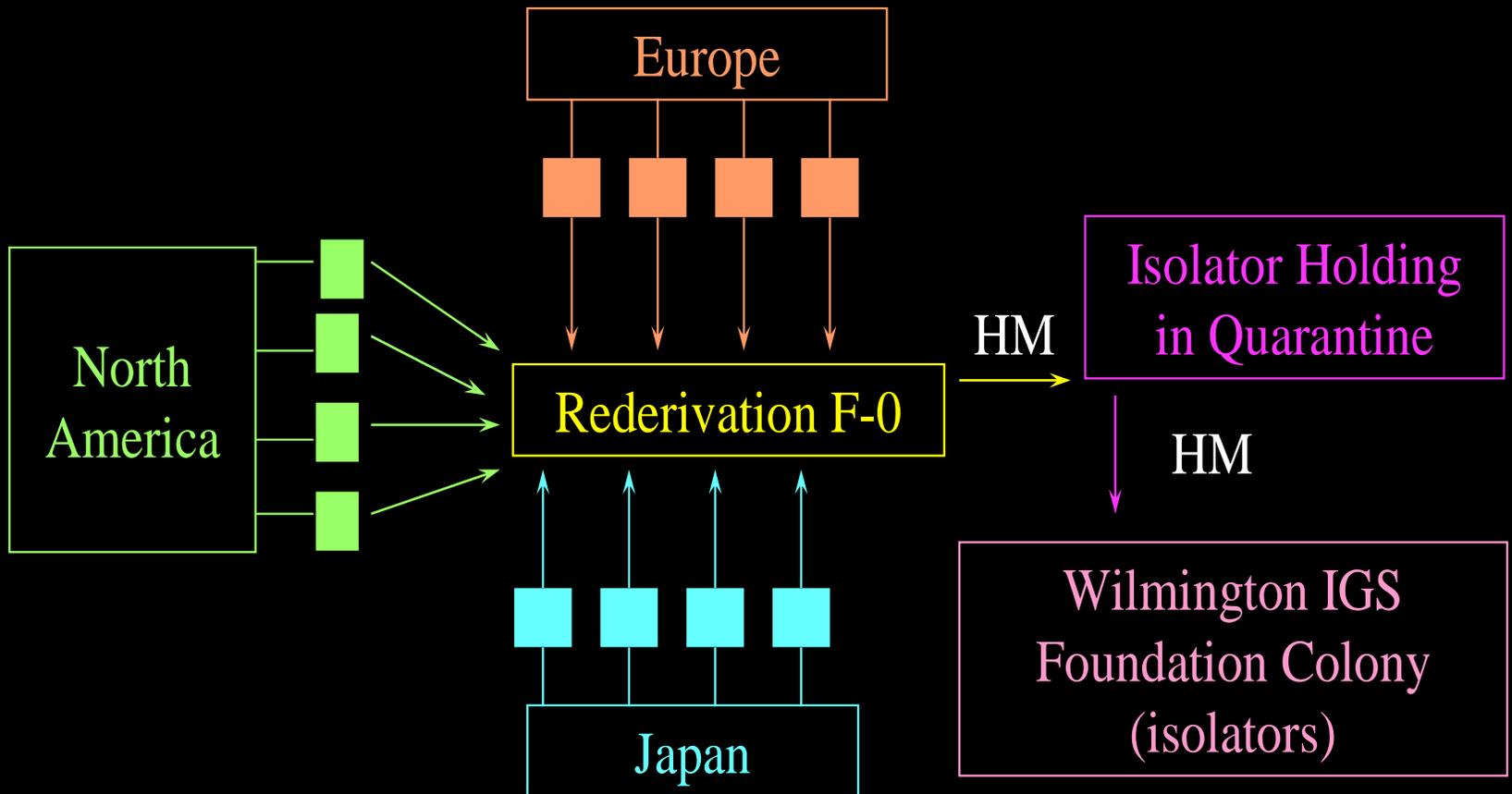




IGS: Forward Migration - Every 3 years



IGS: Backward Migration - Every 5 years



→ Backward Migration: sufficient animals from each production colony to replace 1% of the foundation breeding pairs.

□ = Individual production colonies

Genetic Quality Control of IGS Outbred Stocks

- Genetic Monitoring
 - Unlike inbred or F1 hybrids, outbred stocks cannot be monitored for authenticity
 - With outbred stocks, multiple forms of polymorphic genes are often present in a population, therefore, genetic monitoring results reflect their distribution within the population as well as sample size



How is colony divergence (genetic drift) measured?

- Need to compare variation between colonies based on phenotype or DNA markers
- Can use any polymorphic marker - commonly:
 - Biochemical markers
 - Immunological markers
 - Microsatellites
 - Minisatellites
 - Single nucleotide polymorphisms (SNPs)

