The Role of Nonclinical Data in Assumptions of Extrapolation

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Introduction

- Historically, drug development programs used data from adult animals and humans to support use of a drug in pediatric patients assuming:
  - Similar disease progression
  - Similar response to therapeutic intervention
- However, this approach does not consider growth and developmental differences between adults/pediatric patients, which can have important implications for a drug's pharmacological and toxicological profile.
  - Growth and development may influence drug pharmacokinetics and/or pharmacodynamics
    - Ontogeny of receptors and metabolic functions change with maturity
  - The drug may affect growth and development (a potential safety issue)

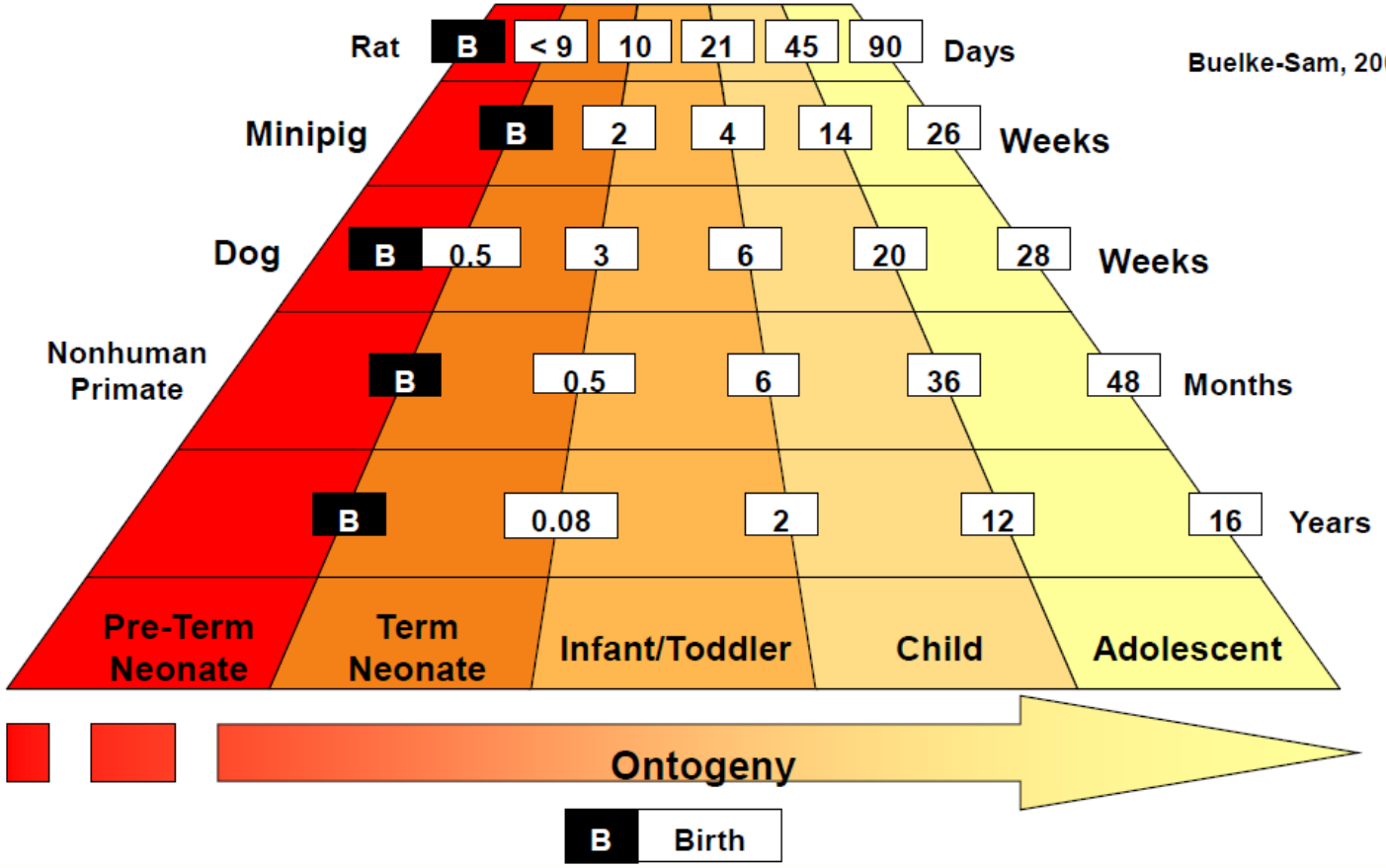
Studies in Juvenile Animals

- Juvenile Animal Studies (JAS) are conducted to evaluate pediatric safety concerns not addressed by adult clinical or standard toxicology studies due to developmental differences
  - Guidance for Industry Nonclinical Safety Evaluation of Pediatric Drug Products, FDA/CDER, 2006
  - Guidance for Industry ICH M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, 2010
- In addition to JAS conducted for safety evaluation, pharmacology studies may be conducted in juvenile animal disease models to demonstrate efficacy.
  - Proof of concept (POC) studies may be needed to support trials in pediatric patients (i.e., to establish a prospect of direct benefit, as per 21 CFR 50, Subpart D) when efficacy data from adults are unavailable

Differences Between Juvenile and Adult Animal Models

- Continued development of organ systems (structural/functional); mature versus immature systems
  - Neurologic, renal, pulmonary, immune, reproductive, skeletal
- Possible differences in pharmacokinetics
  - Absorption, Distribution, Metabolism, Excretion
- Possible differences in pharmacodynamics
  - Receptor expression and function

Comparative Age Categories Based on Overall CNS & Reproductive Development



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- **Indication:** Treatment of irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) in adults
- **Mechanism of Action**: guanylate cyclase-C (GC-C) agonist that acts locally on the luminal surface of the intestinal epithelium
  - Activation of GC-C → ↑ cGMP → Stimulates secretion of chloride and bicarbonate into the intestinal lumen, mainly through activation of the CFTR ion channel → ↑ intestinal fluid and accelerated transit
- **Nonclinical Toxicology:** Compared to adult animals, young mice were shown to be particularly sensitive

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- In neonatal mice, death occurred following 1-2 daily oral doses on PND 7 at 10 mcg/kg, a dose 2000- and 500-times lower than the NOAEL from chronic studies in adult mice and monkeys, respectively
  - » Deaths due to rapid and severe dehydration from significant fluid shifts into the intestinal lumen as a result of GC-C agonism; Supplemental fluid administration prevented death
- In juvenile mice, tolerability to linaclotide increases with age
  - » In 2 and 3 week old mice , single doses of 100 and 600 µg/kg, respectively, produced death
  - » In 4 week old mice, 1000 µg/kg/day for 7 days was well tolerated
  - » In 6 week old mice, 20,000 µg/kg/day for 28 days was well tolerated

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- **Hypotheses for increased sensitivity of neonatal/juvenile mice**
  - Due to increased expression of intestinal GC-C receptors in young animals?*
  - Other factors such as those related to an immature GI system?**
  - Levels of expression of the receptor for heat-stable enterotoxin (i.e., GC-C) in the small and large intestine of children are age-dependent (greater number of receptors present in infants and a decreasing number of receptors with increasing age)***; section 5.1 of the approved labeling states:
    - » "Due to increased intestinal expression of GC-C, children under 6 years of age may be more likely than older children and adults to develop significant diarrhea and its potentially serious consequences."

* Al-Majali et al. Lab Animal Sci, 49: 254-259, 1999; Cohen et al. Pediatri Res, 20: 555-560, 1986
** Walthall et al., Birth Defects Research (Part B), 74: 132-156, 2005; Heller, Arch Dis Child, 25: 195-204, 1951
*** Cohen et al. Gastroenterology, 94: 367-373, 1988.

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- Although this case study specifically demonstrates increased toxicity in juvenile animals, this example also illustrates potential implications of using data from adult animals for extrapolation of efficacy or safety

Pharmacology Studies in Juvenile Animal Disease Models for ERT Development

- Animal models of human disease have been routinely used for establishing POC for enzyme replacement therapy (ERT)
- POC studies needed to support trials in pediatric patients (i.e., to establish a prospect of direct benefit) when efficacy data from adults are unavailable
- Efficacy in juvenile animal disease models may differ from those in adult animals
- There are published reports of improved outcomes in animal disease models when ERT treatment is initiated in juvenile animals (early in life), compared to adult animals; Two examples for mucopolysaccharidoses (MPS) follow

Literature Example – Potential Effects of Age at Initiation of Treatment on ERT Efficacy

- MPS I mice (knockout for α-L-iduronidase) treated with ERT from birth or 2 months of age*
  - Mice treated from birth had better outcomes in aorta and heart valves and reduced antibody levels, compared to mice treated from 2 months of age**
  - Authors suggested the benefit of early treatment is because once structural changes are established in certain organs (e.g., heart), they cannot be reversed

*Baldo et al. Molecular Genetics and Metabolism 2013;109:33-40
**Mice 2 months of age equivalent to human adults (Source: Barrow P.C. 2007)

Literature Example – Potential Effects of Age at Initiation of Treatment on ERT Efficacy

- MPS VII mice (<1% of normal tissue β-glucuronidase (GUS) activity) treated with ERT from birth or 6 weeks of age*
  - Mice treated from birth had less lysosomal storage in some neurons of the brain and skeletal dysplasia, compared to mice treated from 6 weeks of age
  - Authors' hypotheses for reduced response in brain of mice treated from 6 weeks of age:
    - A fixed dose was used, and therefore, older animals had a smaller dose on a mg/kg basis
    - Developmental differences may affect distribution of the enzyme to the brain
    - Downregulation of the mannose-6-phosphate receptor in the brain during postnatal development may contribute to poor uptake of the enzyme

* Sands et al. J Clin. Invest. 1997; 99(7);1596-1605

**Mice 6 weeks of age equivalent to adolescents 12-16 years of age (Source: Barrow P.C. 2007)

Summary

- Use of data from adult animals and humans to support use of a drug in pediatric patients assumes similar disease progression and response to therapeutic intervention
- Importantly, growth and developmental differences between adults/pediatric patients can have important implications for a drug's pharmacological and toxicological profile.
  - Studies conducted in juvenile animals have utility in evaluating pediatric safety concerns and potentially efficacy considerations not addressed by adult clinical or standard toxicology studies in adult animals due to developmental differences.
  - Furthermore, pharmacology studies may be conducted in juvenile animal disease models to demonstrate efficacy and prospect of direct benefit in pediatric patients.