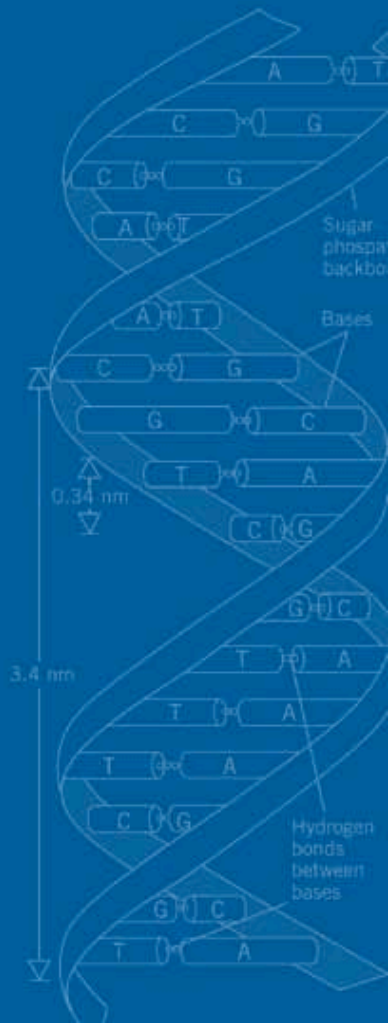
Incorporation of Fertility Endpoints in NHP Chronic Toxicology Studies for mAbs

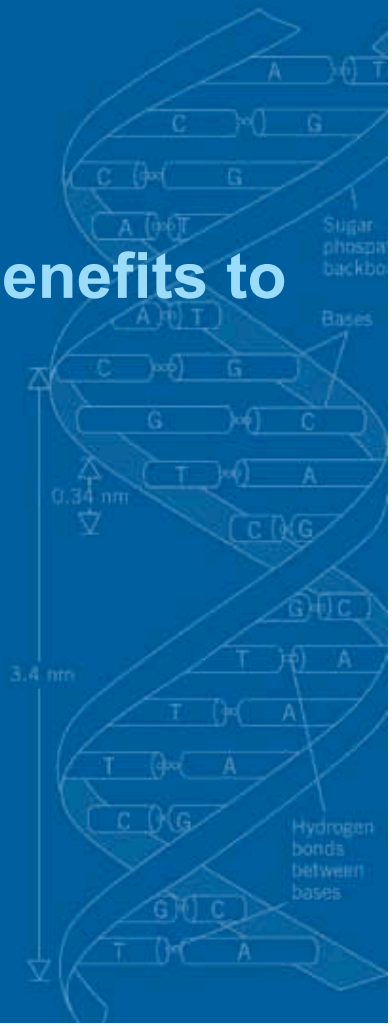
Anu Vaidyanathan, PhD, DABT
Toxicology/ Safety Assessment
Genentech, South San Francisco
May 6th, 2010



Genentech
IN BUSINESS FOR LIFE

Genentech's Strategy and Current Thinking

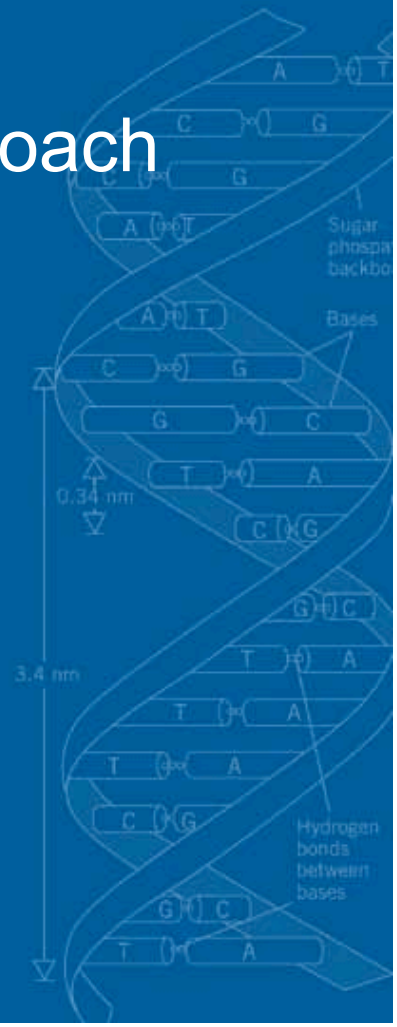
- Evolving change in industry
  - **Many companies have paved the way**
  - **Helped us understand the challenges and benefits to using this approach**
- Results in an optimized study design
- Follows ICH recommended 3 R's



Genentech
IN BUSINESS FOR LIFE

Agenda

- ICH Regulatory Guidance
- Benefits & Strategy: A Combined Approach
- Alternative Approaches
- Conclusions



Genentech
IN BUSINESS FOR LIFE

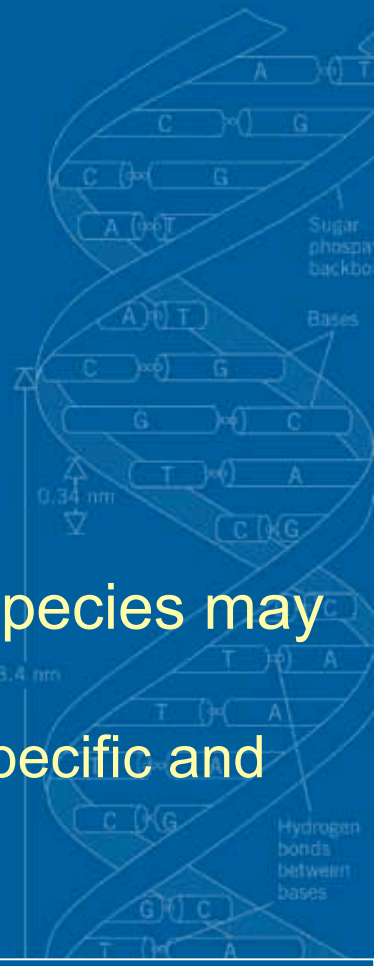
ICH Regulatory Guidance for Fertility Assessment

ICH S5 (R2), S6, M3 (R2)

- ICH S5 (R2): General guideline
  - **At least one species, preferably rats**
  - **Fertility assessment**
    - Pre-mating to conception
      - *–Mating behavior not assessed in NHP models*
    - Conception to implantation
      - *–Not assessed in NHP models*

❖ Issue: NMEs in which rat or alternative rodent species may not be appropriate (Korte et al 1987, 1993; Vogel & Bee 1999; Vogel 2000)

- Many monoclonal antibodies (mAbs) are highly specific and may not recognize rodent/rabbit/dog tissues



Genentech
IN BUSINESS FOR LIFE

NME: New Molecular Entity

For issues unique to biological products

- ICH S6: Guidance for biotechnology-derived pharmaceuticals
  - **Study designs take into consideration:**
    - Species specificity, immunogenicity, half-life and biologic activity
      - Immunogenicity could impact PK/PD
  - **Determine target- dependent effects on fertility**
- Historical control database in both rodents and NHP
- ICH M3 (R2): Applies for recommended timing relative to clinical trials
  - **In general, completed prior to initiation of large scale or long duration trials (i.e. Phase III)**

❖ **Time, cost and resource investment prior to clinical POC**

Genentech
IN BUSINESS FOR LIFE

Benefits to a Combined Approach

- ICH M3(R2) promotion of:

R EDUCE R EFINE R EPLACE

Stand-Alone Fertility

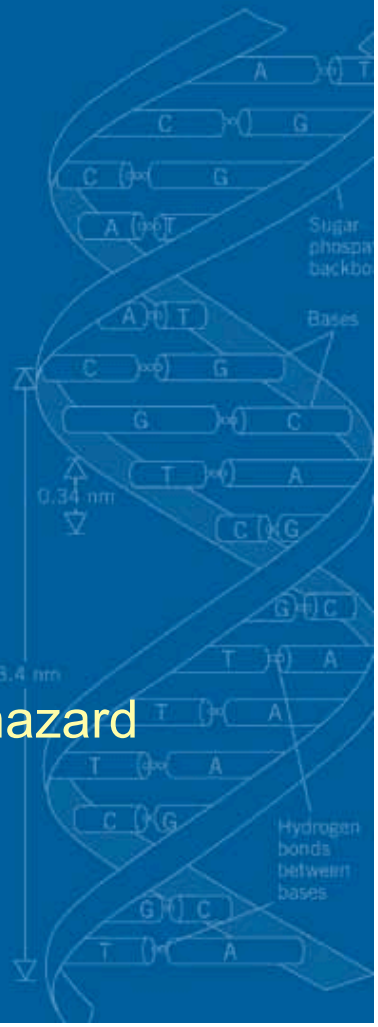
Chronic Toxicology

→ Chronic Tox In Sexually Mature Animals

A Combined Approach

- Decreased animal usage = Less stress on animal supply
- Easily incorporate most endpoints used to identify fertility hazard
- Can generate multiple cycles of data
  - Menstrual or spermatogenic cycles

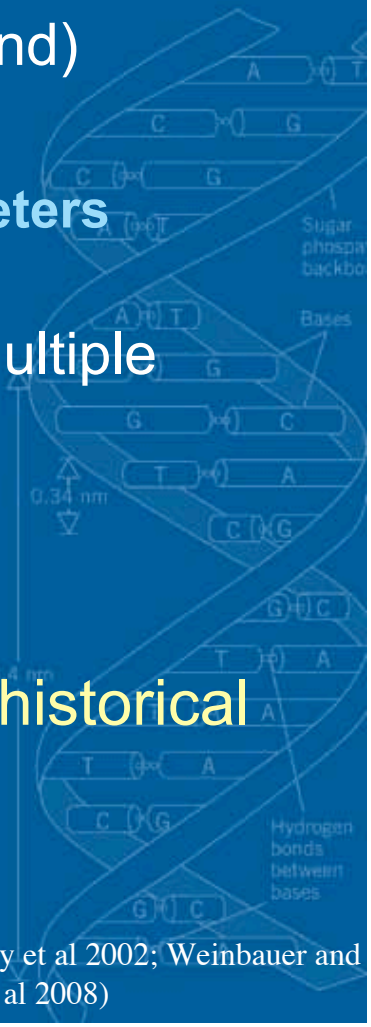
Genentech
IN BUSINESS FOR LIFE



A refined approach: Screening of males

- Age and weight provide reasonable primary screen
  - **Males; ≥ 5-6 ys; ≥ 5 kg (at study start)**
- Testicular volume (as measured by calipers/ultrasound)
- Functional parameters
  - **Serum testosterone, ejaculate volume, sperm parameters (count, motility, morphology)**
- Overall weight of evidence (WOE) approach using multiple factors
  - **Physical & functional parameters**

❖ Ultimately collaborate with CROs experience & historical data to identify sexually mature animals



Genentech
IN BUSINESS FOR LIFE

(Meyer et al, 2006; Smedley et al 2002; Weinbauer and Cooper 2000; Van Esch et al 2008)

Male fertility endpoints in chronic tox study

- Easily incorporate most endpoints used to identify fertility hazard
  - ✓ **Organ wts & histo on reproductive and accessory organs**
  - Prostate, epididymis, seminal vesicles, adrenal & pituitary glands
  - Testes measurement
- Longitudinal effect (semen & hormone analysis)
  - ✓ **Morphology, sperm counts, sperm motility, volume of ejaculate (electro-ejaculation or at necropsy from tail of epididymis)**
    - Collection method could impact endpoints

Genentech
IN BUSINESS FOR LIFE

A refined approach (cont'd)

- ✓ Spermatogenesis staging: Investigation of spermatid development
  - **Represents a continuum of cellular differentiation**
    - Identification of various germ cell types at a specific time point of development
  - **Qualitative**
  - **Appropriately fixed and processed tissues**
- Use weight of evidence (WOE)

❖ Histopathology is acknowledged as a sensitive endpoint for detecting fertility hazard (Sakai et al 2000; Takayama et al, 1995; Creasy, 1997)

Genentech
IN BUSINESS FOR LIFE

A refined approach: Screening of females

- Age and weight provide reasonable primary screen
  - **Females ≥ 4 yrs; 2.5 kg (post-pubertal at study start)**
- Vaginal swabs
  - **Duration of menstrual cycles? Normal vs Abnormal**
    - Presence of regular menstrual cycles?
- Hormone analysis (E_2/PG)
  - **Look for evidence of ovulation**
- Animals not enrolled based on cycle phase
  - **Technically and logistically easier**
- Overall WOE approach using multiple factors
  - **Physical & functional parameters**

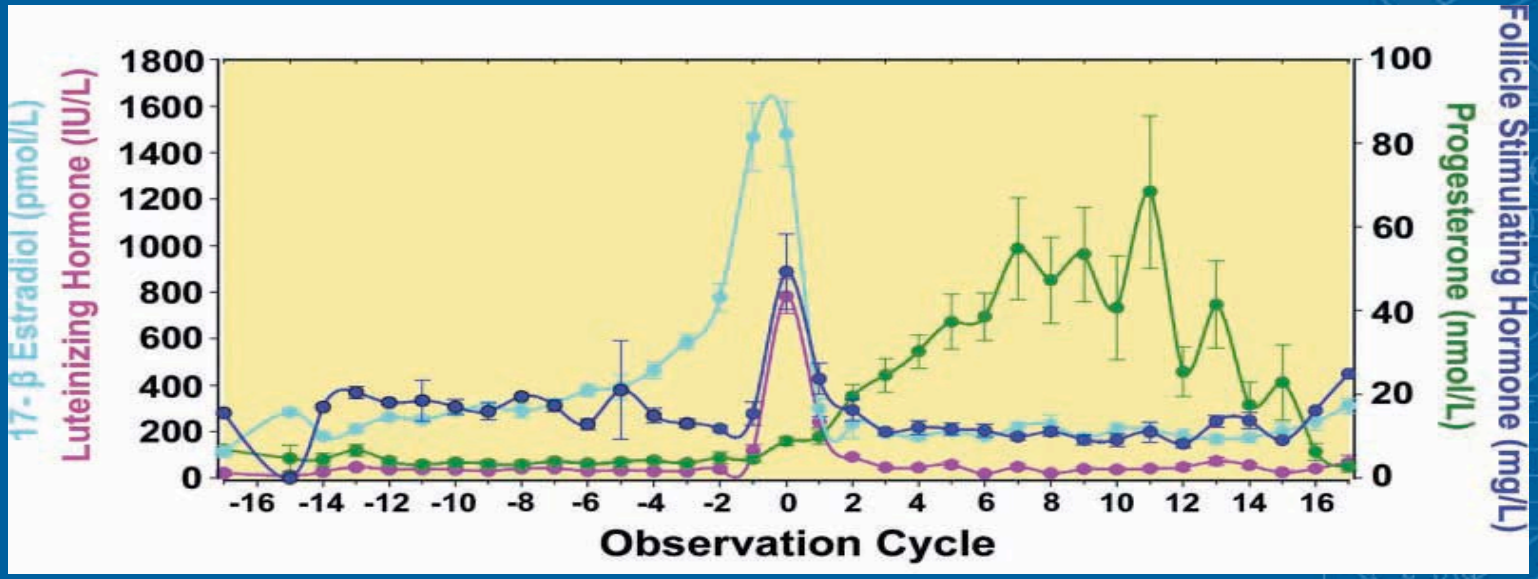
(Meyer et al, 2006; Smedley et al 2002; Weinbauer and Cooper 2000; Van Esch et al 2008)

❖ Ultimately collaborate with CROs experience & historical data to identify sexually mature animals

Female Hormone Cycling

❖ **Frequent blood sampling for female hormone cycling not appropriate for a chronic toxicology study**

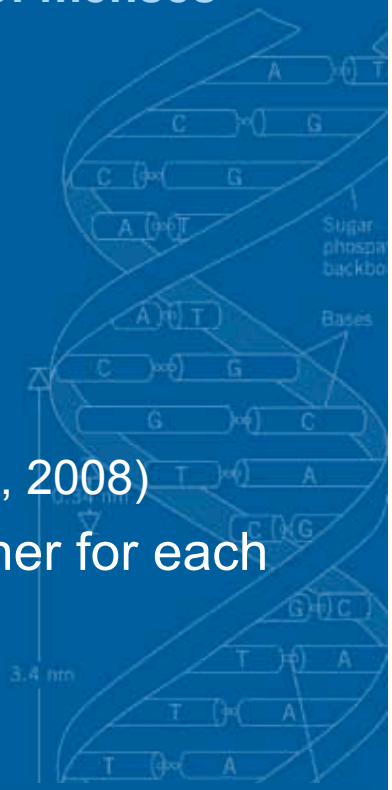
- For accurate/interpretable data need frequent blood sampling (~3 days/cyl)
  - Difficult to reconcile limited hormone data with other endpoints collected for fertility



Genentech
IN BUSINESS FOR LIFE

Female fertility endpoints in chronic tox study

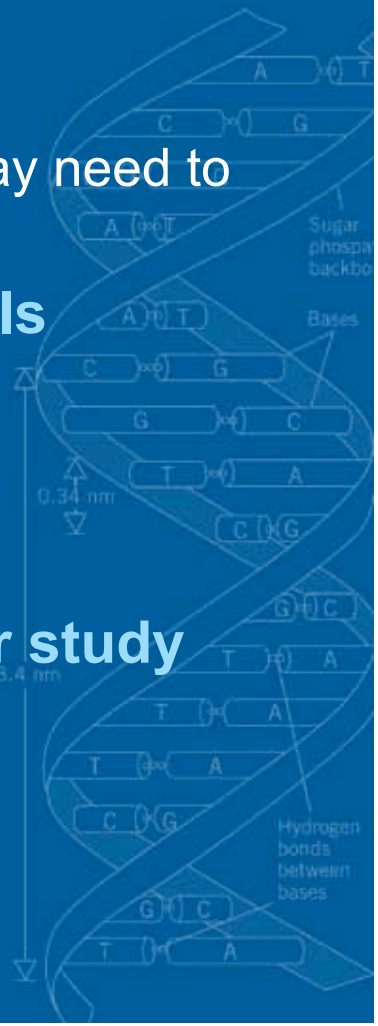
- ✓ Daily vaginal swabs
  - – **Not evaluated for cytology, but for presence or absence of menses**
  - – **Identifies cycle length**
- • Necropsy
  - ✓ **Note general phase of cycle**
  - ✓ **Note sexual maturity status**
    - ▪ Mammary glands
    - ▪ Presence or absence of multiple corpora luteum (CL)
    - ▪ Confirm appropriate endometrial morphology (Van Esch et al, 2008)
  - ✓ Microscopic evaluation of all reproductive tissues together for each animal
    - – **Integrated approach**



❖ Most importantly, in the absence of hormone sampling, a WOE including vaginal swabs and histopathology can be used to detect fertility hazards

Impact on Chronic Toxicology Study

- **A combined approach**
  - **Overall development timeline impact?**
    - Minimal
      - Chronic study planning and implementation efforts may need to initiate sooner
  - **Depends upon supply of sexually mature animals**
  - **Increased screening efforts**
    - Pre-study collections
      - Physical and functional parameters
  - **Screen additional animals to meet required n for study**
  - **Additional cost**
    - ~$170-200K



Genentech
IN BUSINESS FOR LIFE

Limitations to NHP Fertility Evaluation

Mating parameters generally not incorporated

- Low conception rates
  - **2 cycles of mating ~50-90%**
  - **Difficult to power adequately**
- NHP have naturally low fertility rate and high spontaneous abortion rate
  - **Abortion rates of 10-40%, many prior to GD 30**
- Need ~90% reduction in sperm count to see effect on fertility
- No information on conception to implantation
- Not powered to detect infrequent events

Genentech
IN BUSINESS FOR LIFE

Hendrie et al., 1996; Weinbauer et al., 2008; Meyer et al., 2006; Vogel and Bee, 1999; Weinbauer 2002

Data interpretation

Did we identify a hazard?

NO

- Proceed with development
- Additional nonclinical fertility studies not indicated

YES

- Combined approach geared toward hazard identification
  - Will not obtain hormone levels
  - Limited longitudinal data for individually affected animals

Follow-up Targeted Study ***(If not answered in combined approach)***

- Characterize toxic insult
  - Is it consistent with MOA?
  - When did it occur?
  - Determine reversibility and monitorability
  - May need longer recovery phase to determine reversibility

Genentech
IN BUSINESS FOR LIFE

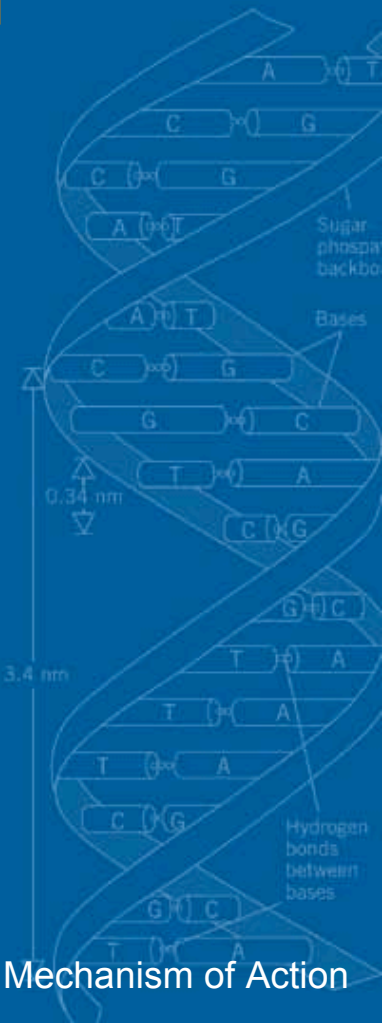
Alternative Strategies: Considerations

Patient Population

- Key demographic
  - Non-life threatening disease
  - Reproductive years
- Oncology vs non-oncology
  - Early stage & adjuvant therapy?

MOA

- Mechanistic role in fertility?
  - Involvement in fertilization/ implantation/placental development
    - Examples
  - Identify on target toxicity to understand mechanism



Genentech
IN BUSINESS FOR LIFE

MOA= Mechanism of Action

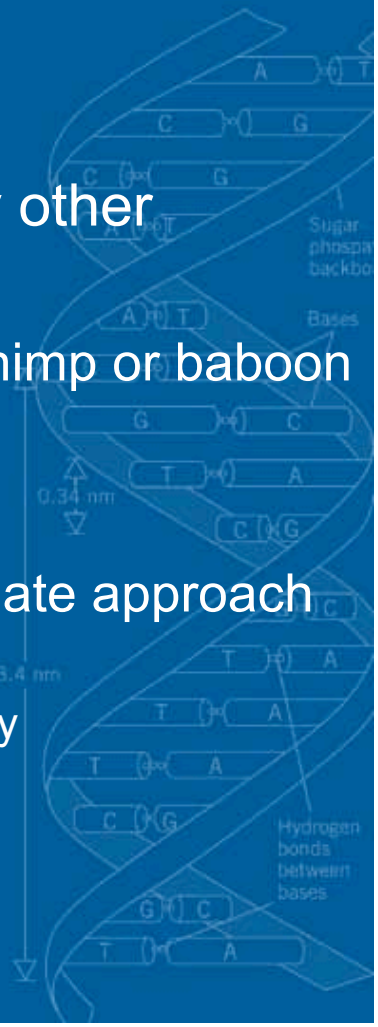
Alternative Strategies: Homolog mAbs

- Use of homologous Abs which cross reacts in rodent
  - **Pros**
    - Study design allows for obtaining data concerning:
      - –Number of successful pregnancies
      - –Impact on mating behavior
      - –Conception and implantation
      - –Multiple offspring
      - –Shorter gestation, higher pregnancy rates and larger number of infants as compared to NHP
      - –Larger number of animals per group to detect trends in the data

Genentech
IN BUSINESS FOR LIFE

Alternative Strategies: Homolog mAbs

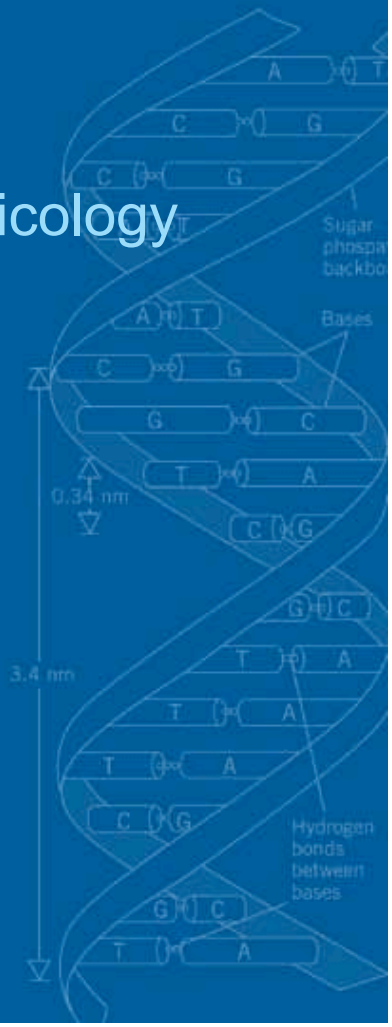
- Use of homologous Abs which cross reacts in rodent
  - **Cons**
    - Validate biology is representative
    - Relevant safety information can not be obtained by other methods
      - Less desirable unless only other binding species is chimp or baboon
    - Will not be testing your clinical candidate
    - Costly & time consuming (Martin et al 2009)
      - Additional validation efforts/assays required by surrogate approach
        - Biochemical characterization
        - Measurement of serum/plasma levels & potential immunogenicity
        - Separate manufacturing process



Genentech
IN BUSINESS FOR LIFE

Legacy Projects for mAbs

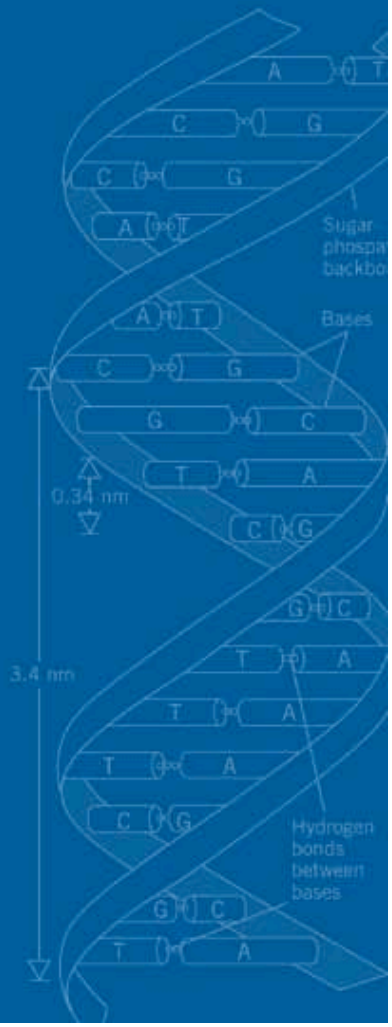
- Late stage development project
  - May have already conducted chronic tox study
- Considering the patient population & MOA
  - Were sexually mature animals used in general toxicology studies?
    - Histopathology on reproductive and accessory organs
- KO mating data available?
- Tissue cross reactivity
  - Binding in reproductive tissues?



Genentech
IN BUSINESS FOR LIFE

Clinical Fertility Assessment

- Clinical fertility endpoints may be acceptable by regulatory agencies
  - Good subject to address with agency
- Data generated
  - Endocrine, sperm and menstrual data
- Timing of fertility evaluation depends upon
  - Size of trial
  - Indication
  - Patient population
- May impact patient enrollment?



Genentech
IN BUSINESS FOR LIFE

Conclusions

- Can easily incorporate most endpoints used to identify fertility hazard into chronic tox study designs
  - **May need follow-up if a fertility hazard is identified**
- Several criteria exist to ensure enrollment of sexually mature animals for general tox studies
  - **Ultimately rely upon CRO guidance**
- Alterative strategies exist, use case by case approach
  - **Consider stage of development**
  - **Patient population**
  - **MOA**
- Encourage open dialogue when possible with regulatory agencies when using alternative approaches

Genentech
IN BUSINESS FOR LIFE

Acknowledgements

Key Contributors

Genentech

- Tom Gelzleichter
- Wendy Halpern
- Theresa Reynolds
- Noel Dybdal

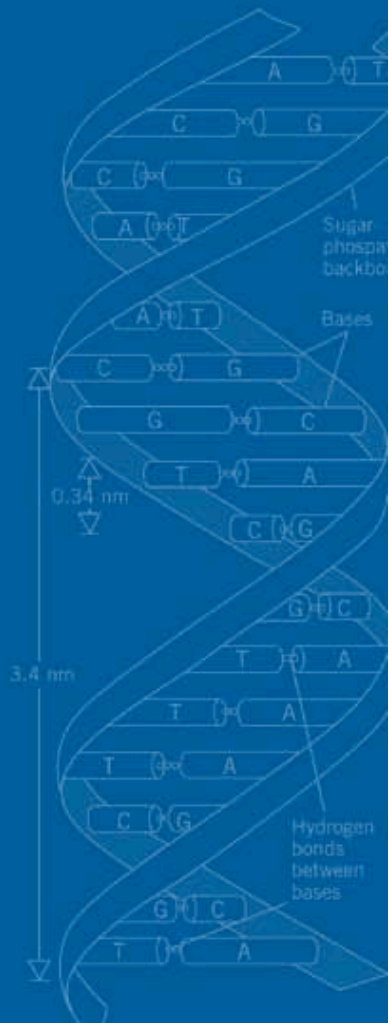
Charles River Laboratories, Reno

- Diana Auyeung-Kim
- Julie Meyer

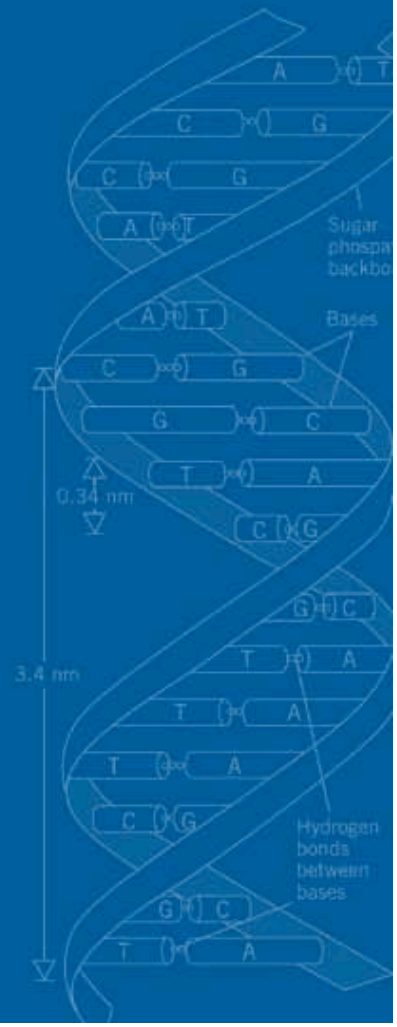
Thought Leaders

- E Buse
- R Korte
- D Creasy
- HC Dreef
- J Vidal
- S Rehm
- F Vogel
- TA Hendrie
- AG Hendrickx
- J Cavagnaro
- A Hoberman
- E Van Esch
- GF Weinbauer
- GJ Chellman
- PL Martin
- W Bee
- JM Cline

Genentech
IN BUSINESS FOR LIFE



Appendix



Genentech
IN BUSINESS FOR LIFE

References

- Weinbauer GF, Niehoff M, Niehaus M, Srivastav S, Fuchs A, Van Esch E and Cline JM. Physiology and endocrinology of the ovarian cycle in Macaques. Toxicol Pathol 2008; 36; 7S.
- Van Esch E, Cline JM, Buse E, Weinbauer GF. The Macaque endometrium, with special reference to cynomolgus monkey (Macaca fascicularis). Toxicol Pathol 2008; 36; 67S.
- Van Esch E, Cline JM, Buse E, Wood CE, De Rijk EPCT, Weinbauer GF. Summary comparison of female reproductive system in human and the cynomolgus monkey (Macaca fascicularis). Toxicol Pathol 2008; 36:171S-172S.
- Weinbauer, GF. 2002. The non-human primate as a model in developmental and reproductive toxicity. In: Weinbauer, GF, Korte, R, editors. *Reproduction in nonhuman primates*. Munster, Germany: Waxmann Verlag GmbH. p 49-66.
- Weinbauer GF. 2005. Reproductive/developmental toxicity studies in the cynomolgus monkey: How close are we to human? In: Weinbauer GF, Buse E, Muller W, Vogel F, editors. *New developments and challenges in primate toxicology*. Munster, Germany: Waxmann Verlag GmbH. p 88-95.
- Weinbauer GF, Cooper TG. 2000. Assessment of male fertility impairment in the macaque model. In: Weinbauer GF, Korte R, editors. *Towards new horizons in primate toxicology.* Munster, Germany: Waxmann Verlag GmbH. p 13-42.
- Korte R, Weinbauer GF ed (1999). *Reproduction in nonhuman primates*. Munster, Germany: Waxmann Verlag GmbH.

Genentech
IN BUSINESS FOR LIFE

References

- Vogel F. 2000. How to design male fertility investigations in the cynomolgus monkey. In: Weinbauer GF, Korte R, editors. *Towards new horizons in primate toxicology*. Munster, Germany: Waxmann Verlag GmbH. p 43-52.
- Vogel F, Bee W. 1999. Reproductive toxicology in primates: An overview of methods and techniques. In: Weinbauer GF, Korte, R, editors. *Reproduction in nonhuman primates*. Munster, Germany: Waxmann Verlag GmbH. P 95-110.
- Hendrie TA, Peterson PE, Short JJ, Tarantal AF, Rothgarn E, Hendrie MI, Hendrickx AG. Frequency of prenatal loss in a macaque breeding colony. *Am J Primato*l 1996; 40:41-53.
- Dreef HC, Van Esch E, De Rijk EPCT. Spermatogenesis in the cynomolgus monkey: A practical guide for routine morphological staging. *Toxicol Pathol* 2007; 35: 395-404.
- Meyer JK, Fitzsimmons D, Hastings TF, Chellman GJ. Methods for the prediction of breeding success in male cynomolgus monkeys (macaca fasiculararis) used for reproductive toxicology studies, *J Am Assoc Lab Animal Sc*i 2006; 45:31-36.
- Smedley JV, Bailey SA, Perry RW, O'Rourke CM. Methods for predicting sexual maturity in male cynomolgus macaques on basis of age, body weight and histologic evaluation of the testes. *Contemp Top Lab Anim Sci* 2002; 41(5): 18-20.
- Creasy DM. Evaluation of testicular toxicology: A synopsis and discussion of the recommendations proposed by the Society of Toxicologic Pathology. *Birth Defects Research* (Part B) 2003; 68:408-415.
- Creasy, D. M. (1997). Evaluation of testicular toxicity in safety evaluation studies: The appropriate use of spermatogenic staging. *Toxicol* Pathol 25,119– 131.

Genentech
IN BUSINESS FOR LIFE

References

- Sakai T, Takahashi M, Mitsumori K, Yasuhara K, Kawashima K, Mayahara H, Ohno Y. Collaborative work to evaluate toxicity on male reproductive organs by repeated dose studies in rats-Overview of the studies. *J Tox Sci* 2000; 25:1-21.
- Weinbauer GF, Frings W, Fuchs A, Niehaus M, Osterburg I. 2008. Reproductive/developmental toxicity assessment of biopharmaceuticals in nonhuman primates. In: Cavagnaro JA, editor. *Preclinical safety evaluation of biopharmaceuticals*. Hoboken, NJ: John Wiley & Sons. P 379-397.
- Takayama S, Akaike M, Kawashima K, Takahashi M, Kurokawa Y. A collaborative study in Japan on optimal treatment period and parameters for detection of male fertility disorders induced by drugs in rats. *J Amer College Tox* 1995; 14(4):266-292.
- Korte R, Vogel F, Osterburg I. The primate as a model for hazard assessment of teratogens in humans. *Arch Toxicol Suppl* 1987; 11: 115-121
- Korte R, Vogel F, Bee W, Osterburg I. 1993. The use of the non-human primate in reproduction toxicology. In: Korte R, Fanghanel J, Gossrau R, editors. *Teratologie- Embryologische Grundlagen, experimentel-le und klinische Teratologie*. Berlin/ New York: Walter de Gruyter. P 167-191.
- Vogel F. 2000. How to design male fertility investigations in the cynomolgus monkey. In: Weinbauer GF, Korte R, editors. *Towards new horizons in primate toxicology.* Munster, Germany: Waxmann Verlag GmbH. p 43-51.
- Martin PL, Breslin W, Rocca M, Wright D, Cavagnaro J. Considerations in assessing the developmental and reproductive toxicity potential of biopharmaceuticals. *Birth Defects Res (Part B)* 2009; 86:176-203.

Genentech
IN BUSINESS FOR LIFE

Utility of NHP Model for Fertility Assessment

Pros

- Physiology of menstrual cycle & endocrine systems of NHP similar to human
  - Similar parameters used to investigate fertility clinically
- Allows for collection of larger blood volumes
  - Potential use of biomarkers of toxicity for direct comparison to clinical endpoints

(Reviewed in Weinbauer 2005; Van Esch et al. 2008; Korte & Weinbauer 1999)

Cons

- Limited to assessment of estrous cycling and hormonal profiles
  - No data regarding mating behaviors, conception to implantation
- Generally underpowered as compared to rodent fertility studies

Genentech
IN BUSINESS FOR LIFE

An example…

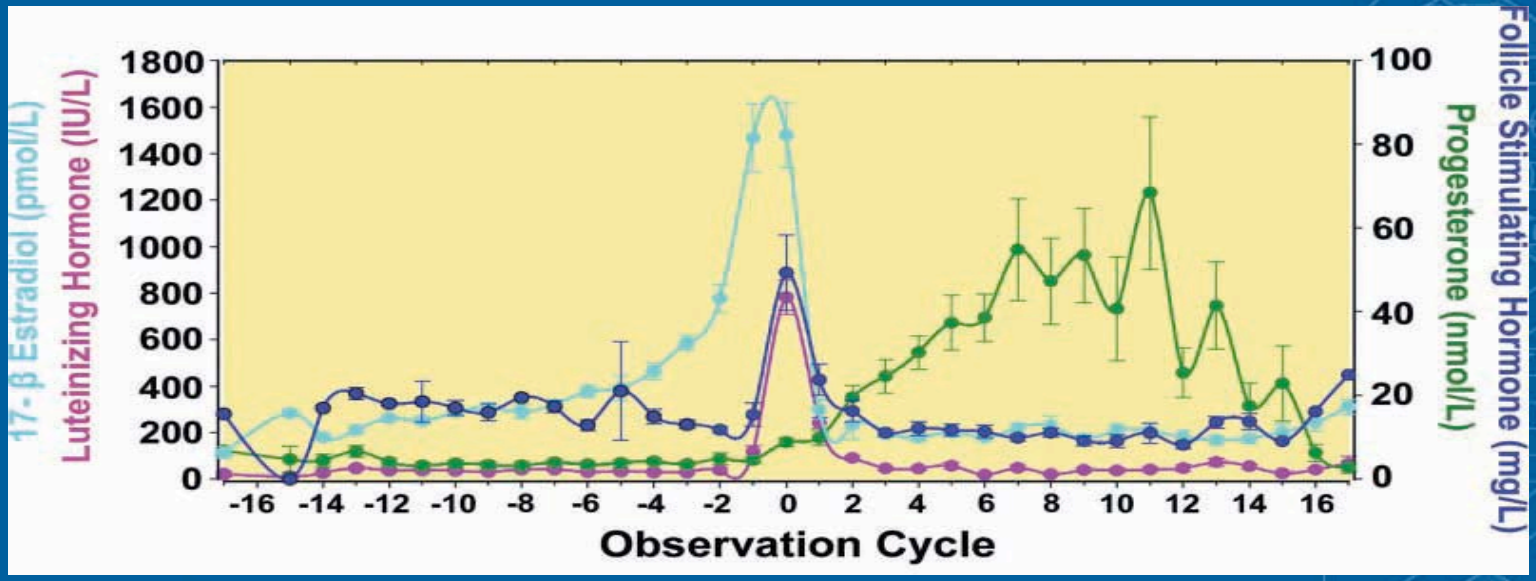
FEMALE STAND-ALONE NHP FERTILITY

3 mos cycle check	3 mos dosing phase	3 mos recovery*

Endpoints evaluated:

- Vaginal swabs
- Blood collections for estrogen and progesterone cycling data (every 3 days/cycle)
- Histopathology- provides mechanism, histo may not add much value if no cycle abnormalities

* Recovery dependant upon drug clearance
1 mens. cycle ~ 28 days +/- 8 days; consider synchronized dosing



Follicular Phase | Ovulation | Luteal Phase

(Weinbauer et al., 2008)

Genentech
IN BUSINESS FOR LIFE

An example…

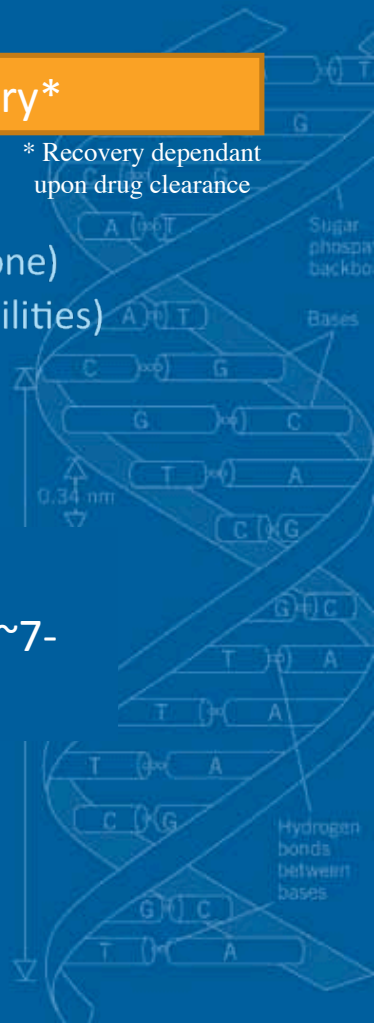
MALE STAND-ALONE NHP FERTILITY

1 mo pre-dose ck	2 mos dosing phase	4 mos recovery*

* Recovery dependant upon drug clearance

Endpoints evaluated:

- organ wts & histo (prostate, epididymis, seminal vesicles, adrenal & pituitary glands)
- testes measurement
- semen analysis
- hormonal assessment (testosterone) (different labs have different capabilities)
- Spermatogenic staging



<u>Justifications / Assumptions</u>

- Dosing for 1 spermatogenic cycle ~40-45 days; epididymal transit time ~7-10 days *(Creasy, 2003)*

Genentech
IN BUSINESS FOR LIFE