

Translational Animal Modeling: A critical step in pediatric medical device development



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What is this talk about?

- What are we modeling in pediatrics?
- Definitions – translational, models, animals
- Strengths of a translational approach
- Weaknesses of a translational approach
- Practical considerations: An example
- Questions and (maybe) answers

Pediatric

- Defined – (American College Dictionary, 1963)
- Greek “*paidi*” – child
- Greek “*iatrikos*” – medicine
- “The science of the medical and hygienic care of, or the diseases of, children”



Stages of childhood

- A continuum of development that really has different stages and problems
- Advancement through stages is very individualized
 - *In utero* development
 - Newborns (up to 1 year?)
 - Young children (up to 5 years?)
 - Older children (up to 10 years?)
 - Adolescents (up to 15 years?)
 - Late adolescents (up to 20 years?)
 - Adult children living at home



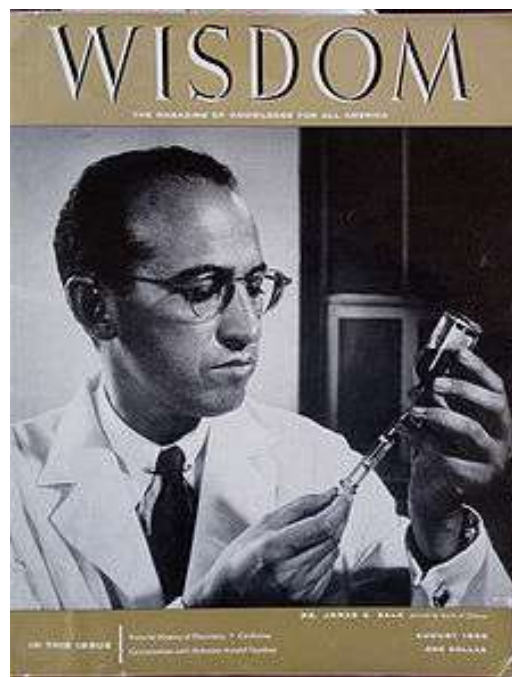
What are the determinants of “childhood”?

- Chronologic age
- ***Brain physical and functional maturation***
- ***Physiologic maturation and ability to adapt***
- ***Immunologic maturity/exposure/vaccination***
- “Tool-making” and problem-solving; social adaptation
- ***Achievement of adult body size and functions (reproductive maturation)***
- *Independence*

Common pediatric health problems

- [ADHD](#)
- [Autism](#)
- [Birth defects\(1/33 children – ACOG\)](#)
- [Dental caries](#)
- [Candidiasis \("Thrush"\)](#)
- [Chagas disease](#)
- [Chickenpox](#)
- [Congenital Heart Disease](#)
- [Croup](#)
- [Cystic Fibrosis](#)
- [Cytomegalovirus](#)
- [Diabetes mellitus – Type I](#)
- [Diphtheria](#)
- [Duchenne muscular dystrophy](#)
- [Fifth disease](#)
- [Hand, Foot, Mouth Disease](#)
- [Hepatitis A](#)
- [Herpesvirus infection](#)
- [Influenza](#)
- [Leukemia](#)
- [Lyme Disease](#)
- [Measles](#)
- [Molluscum contagiosum](#)
- [Mononucleosis](#)
- [Mumps](#)
- [Osgood-Schlatter's disease](#)
- [Polio](#)
- [Rheumatic fever](#)
- [Rickets](#)
- [Roseola](#)
- [Rubella](#)
- [Scarlet fever](#)
- [Sever's disease](#)
- [Tetanus](#)
- [Whooping cough](#)





Translational modeling

- ***Definition #1:*** The discovery of knowledge in the laboratory (The Bench) that is used for treating sick patients (The Bedside)
- ***Definition #2:*** The study of the effects of drugs or devices in surrogates (healthy animal) to predict the effects in sick patients
- ***Definition #3:*** The study of a disease process in a surrogate (sick animal) that will lead to the discovery of knowledge that is used for treating sick patients

Why use surrogate animals for modeling pediatric diseases?

- Anatomy, physiology and metabolism (health) is analogous to humans
- Defined characteristics (genetics, environment, patterns of spontaneous disease)
- Readily-available for ethical use
- ***Wide range of sizes available ->growth***
- ***May have highly homologous disease processes***

Translational modeling assumptions

- The study of the effects of drugs or devices in surrogates (healthy animals) ***predicts*** the effects in sick patients
 - Example: preclinical testing of virtually all pharmaceuticals and biologicals is done almost exclusively in healthy rodents and at least one other species

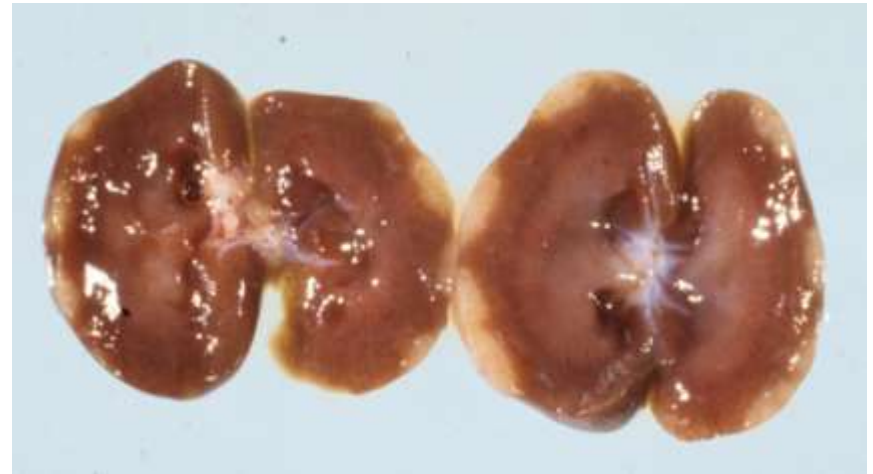
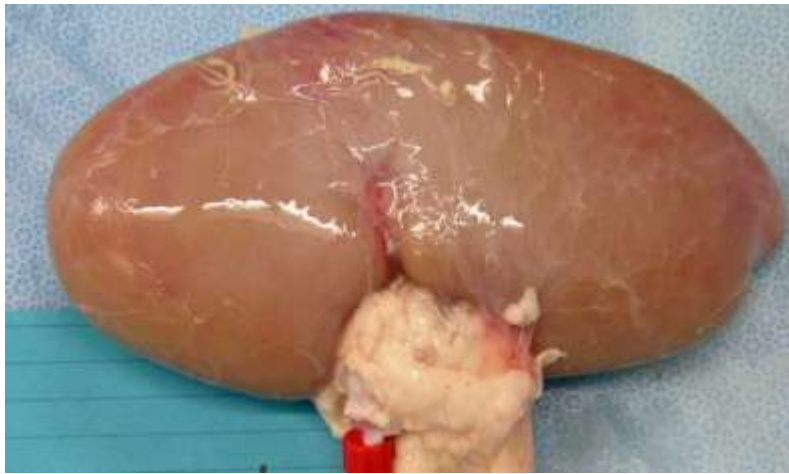


Healthy animals = Sick people

- Anatomy, physiology, metabolism, pharmacokinetics of healthy mammals are predictable and well-known
- These are *comparable*, on a body size and maturational basis, to humans
- Works 95% of the time (See next slide)
- Works better than lower vertebrates or cell cultures

Exceptions (Healthy animals = Sick people)

- Spontaneous pathology in model species may not be same as spontaneous pathology in people



Exceptions (Healthy animals = Sick people)

- Spectrum of disease in models may not be the same as people
 - Rat neoplasms: Benign mammary tumors, pituitary tumors, lymphoma
 - People: Mammary cancer, prostate cancer, lung cancer



Exceptions (Healthy animals = Sick people)

- Average animal lifespan compared to human lifespan? ***Is this a sound concept?***
 - Mouse year (1 mouse year = 38 human years)
 - Poodle year (1 Poodle year = 5 human years)
 - Great Dane year (1 GD year = 9 human years)
 - Macaque year (1 Rhesus year = 2 human years)
- If so, what is animal “childhood”?



Translational modeling assumptions

- The study of a disease process in a surrogate (sick animal) *will* lead to the discovery of knowledge that is used for treating sick patients
 - Spontaneous disease = occurs and progresses in animal species as a result of natural processes and environmental influences
 - Induced disease = occurs and progresses in animal species as a result of human intervention

Sick animals

- Spontaneous disease



Elderly Foxhound with multiple mammary gland tumors

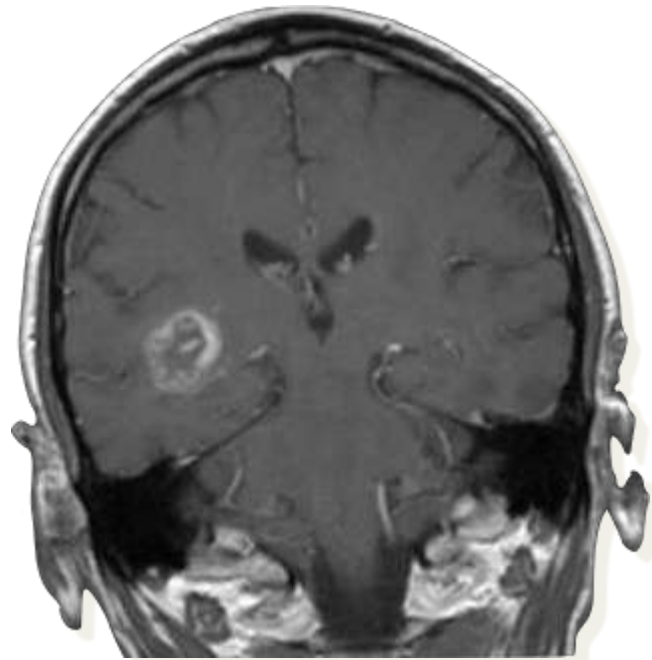
- Induced disease



Athymic mouse with subcutaneous human malignant glioma

A good example: Malignant gliomas

- Group of highly aggressive primary brain tumors
- Leading cause of cancer death in children
- Median (child and adult) survival 15 months
- 2-year mortality is 95%
- In last 70 years of research, life expectancy \uparrow 7 months
- Resistant to most chemo & radiation



Dogs are an excellent translational model for malignant glioma

- 3x more common in dogs than people
- Very similar properties
 - Genetics
 - Pathology
 - Invasiveness
- Accelerated course of the disease
- Clinical signs same as people
- Adult onset in dogs and people
- Limited treatments

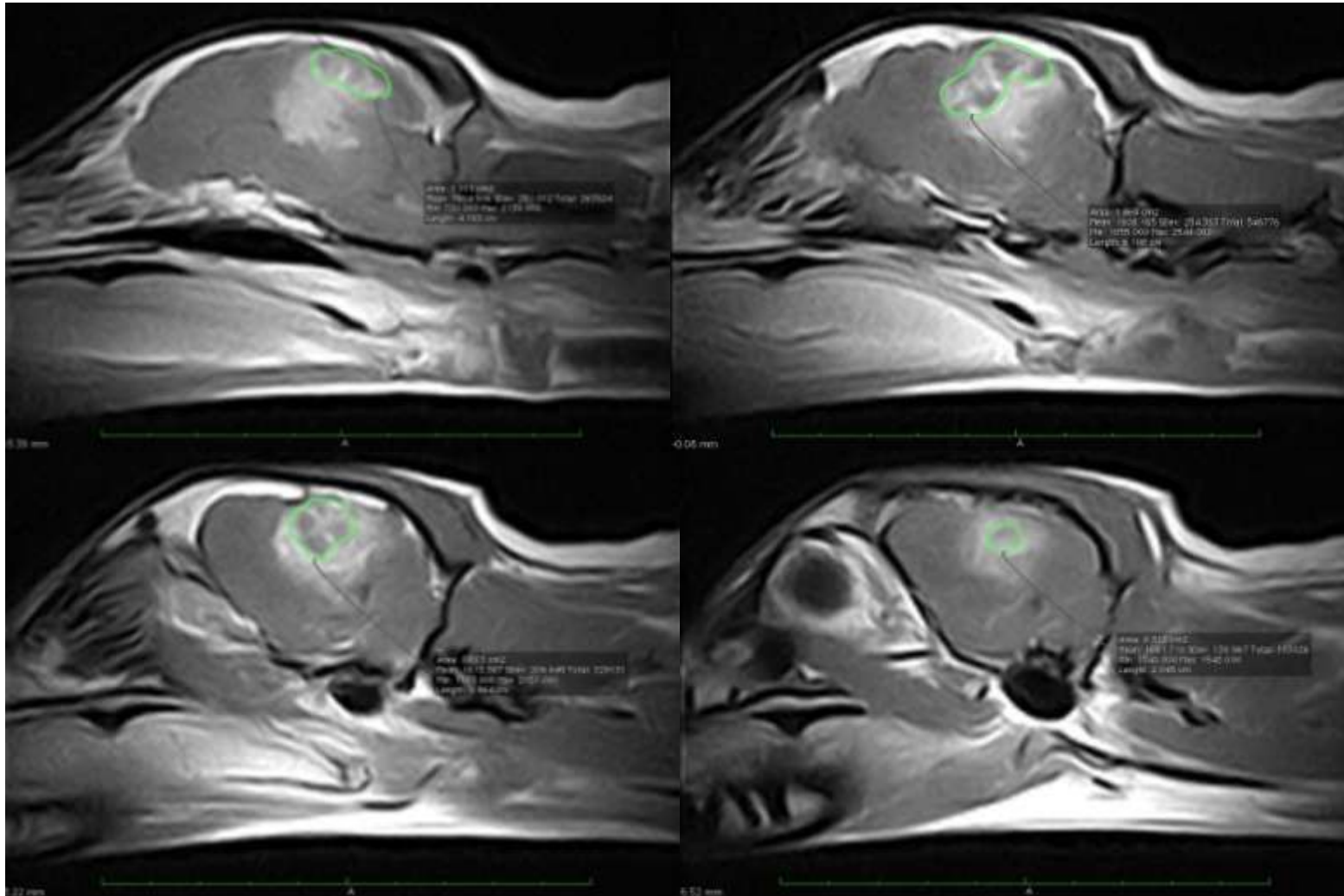


Patient: High grade glioma treatment

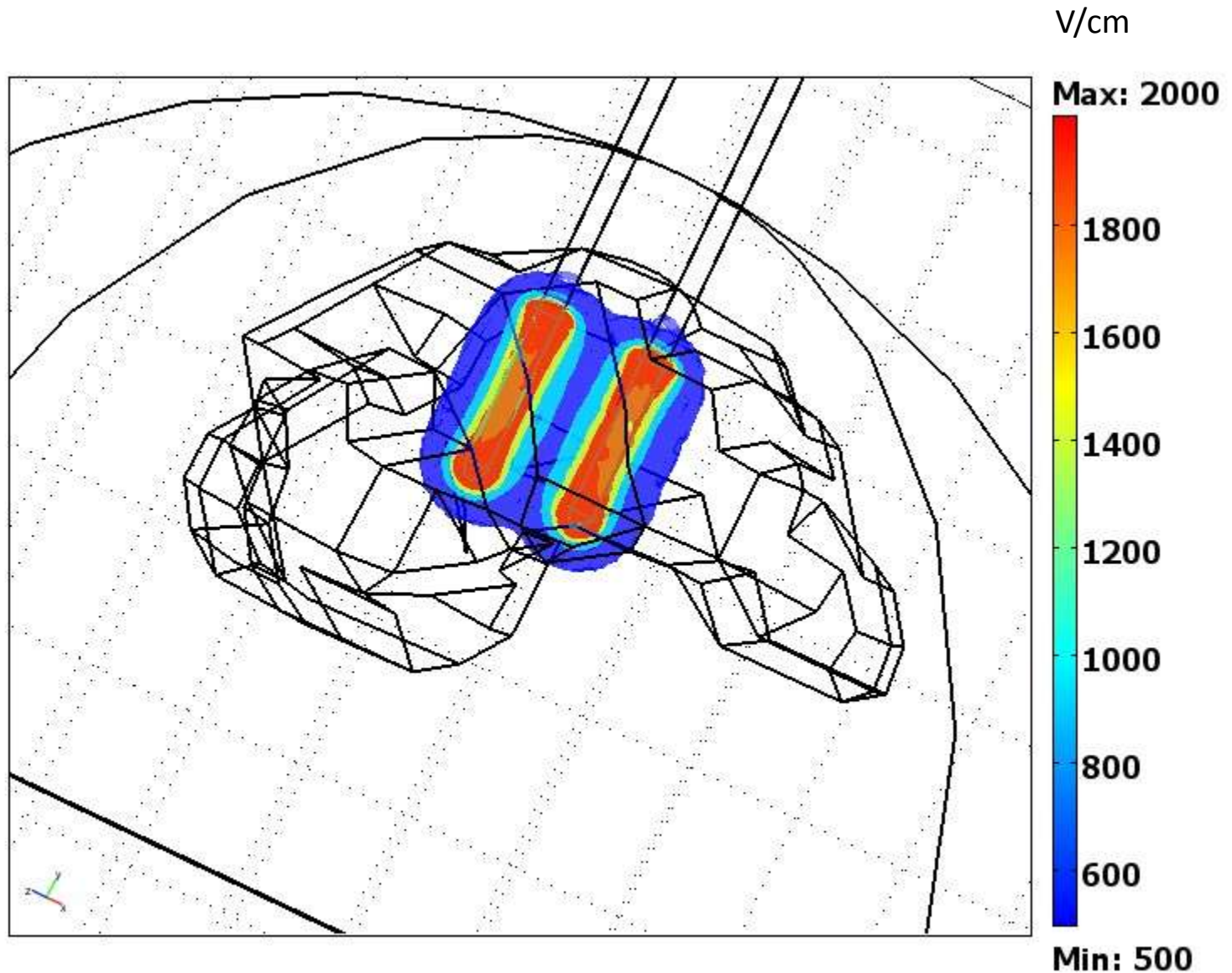
- Severely affected clinically for radiation therapy (RT).
- Tumor and edema are clearly visible in MRI.
- Determined inoperable at time of biopsy
- Severe ventricle compression
- Increased intracranial pressure



IRE Treatment Protocol for High-grade Glioma Canine Patients



Treatment Planning: Reconstructed Tumor Geometry Imported into Numerical Software.



MRI of canine brain cancer patient

Pre IRE

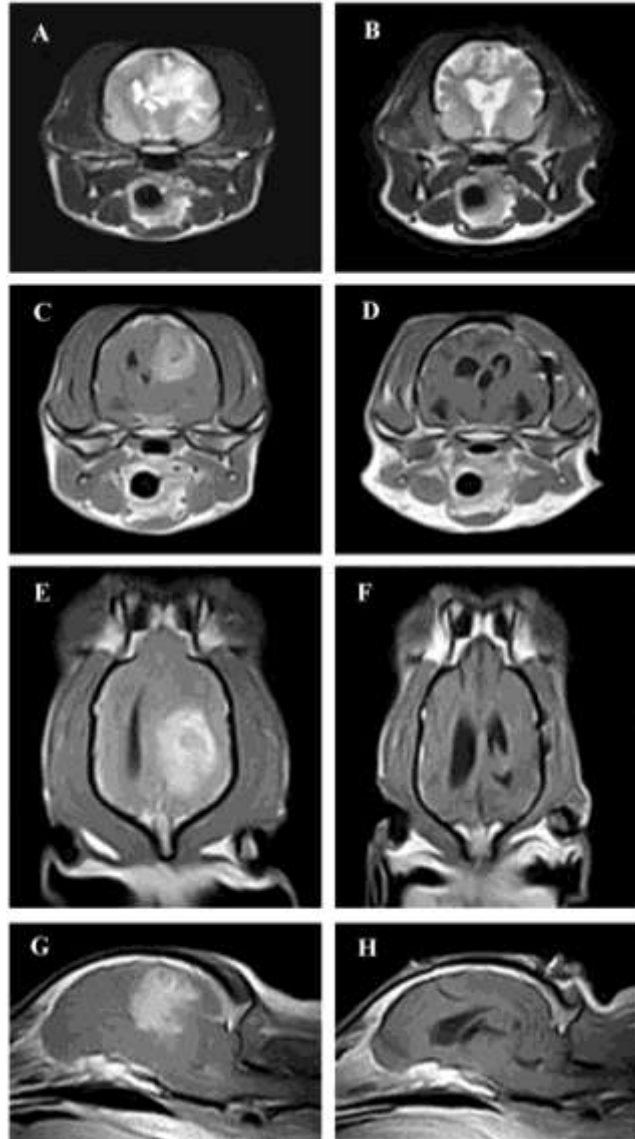
Severely affected clinically for RT.

Tumor and edema are clearly visible.

Inoperable High-grade Tumor.

Severe Ventricle Compression.

Increased Intracranial Pressure.



4 months post IRE

Tumor has completely regressed.

No evidence of edema.

Ventricles severely decompressed.

Reduced Intracranial Pressure.

Extended and improved quality of life.

Characteristics of a good translational model - summary

- Most characteristics of model and target of modeling are identical or very similar
- Most characteristics of disease in model and target of modeling are identical or similar
- Disease in model and target are studied at comparable ages and developmental stages
- Results of modeling are highly reproducible
- ***Practical considerations are VERY important***
 - Size of model must be appropriate for translation (Can a mouse wear a stereotactic head frame for brain surgery?)
 - Growth, growth, growth
 - Morbidity and mortality management must be achievable
 - Availability of model and facilities to do sophisticated work will limit research

Thank you! Questions?



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