Challenges of Developing Therapeutics for Children

Children are not just small adults and come in all sizes with different challenges

Challenges in Children Compared to adults

- The nature of the disease can be different, requiring different endpoints.
- There are more restrictions on pediatric trials; for example, the volume of samples that can be taken requires more innovative statistical design.
- There are additional safety considerations, such as growth and development, in pediatric trials.
- “Pediatric” patients include neonates through adolescents, with very different considerations for each age group.
- The formulation of a drug needs to be different for younger and older patients.
- The expertise needed for pediatric trials often is not available in house, so external experts need to be consulted.

Challenges

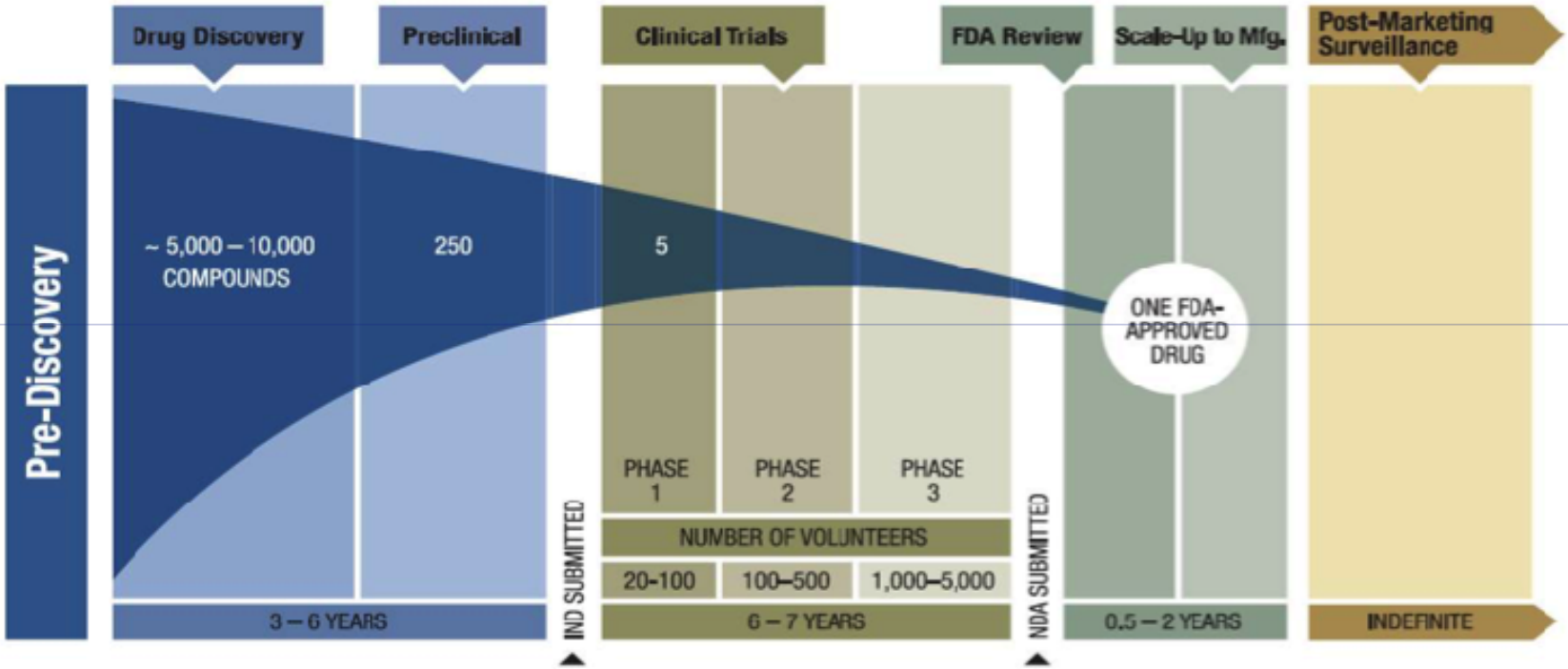
- These differences include the ways in which medicines are adsorbed, distributed, metabolized and excreted by the body (pharmacokinetics) and what medicines do to the body (pharmacodynamics)
- Children are often unable to take the dosage forms that are designed for adults.

- Moreover diseases in children are often different from their adult equivalents. The processes underlying growth and development might lead to a different effect and response to drug unseen in adults. Particularly, children at various ages might be exposed to different risk/benefit ratios. Thus, children are not small adults. Indeed, pharmacologically speaking infants are not small children. Important medicines need to be tested in each target population

More Challenges

- Finding patients to enter a clinical trial is difficult
- Informed consent is more difficult
- Parents may not be able to take a child to a clinical research center that may be some distance away.
- Parents may not be able to take a large number of days off from work

Drug Discovery and Development Timeline



Regulatory Issues Designed to Improve Research US

- The Best Pharmaceuticals for Children Act (BPCA) provides an incentive for drug companies to conduct FDA-requested pediatric studies by granting an additional six months of marketing exclusivity.

- The Pediatric Research Equity Act (PREA) requires drug companies to study their products in children under certain circumstances. When pediatric studies are required, they must be conducted with the same drug and for the same use for which they were approved in adults.

- Before BPCA and PREA became law, more than 80% of the drugs approved for adult use were being used in children, even though the safety and effectiveness had not been established in children. Today that number has been reduced to about 50%.

Regulatory Issues designed to Improve Research EU Global

- At the end of 2006, an EU Pediatric Regulation (Reg 1901/2006/EU and Reg 1902/2006/EU) was adopted with a similar scope and a different implementation mechanism than the US legislation. Like the US legislation, the goals focus on improving children's health through advancements in research and on providing a new framework for an efficacious and safe use of pediatric drugs.

- In 1999, 20% of new medical entities relevant to pediatrics had pediatric information while between 2002 and 2008 41% had pediatric information. In 1973 this publication had pediatric information on 22% of products and in 2009 the figure was 46% .

Rare Diseases

- There are thousands of rare diseases that occur primarily in children that cause debilitating morbidity and mortality.
- The populations in each disease are usually to small to study in a clinical trial
- The majority of diseases are genetic defects due to gene mutations

Vanessa Research
Microvillus Disease in Children

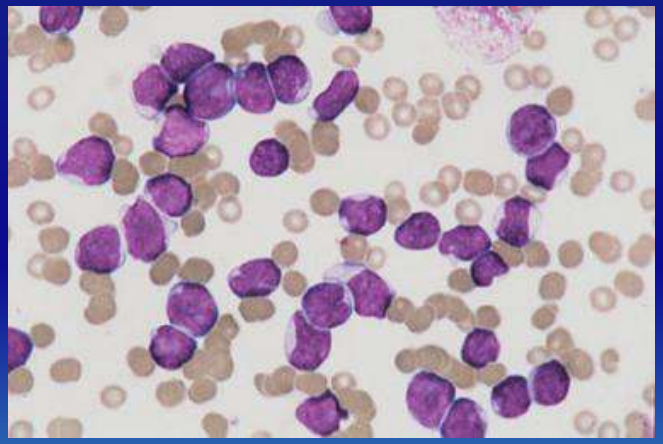
With all of the Challenges can we make any progress in Childhood drug development ???

Progress in Childhood Cancers

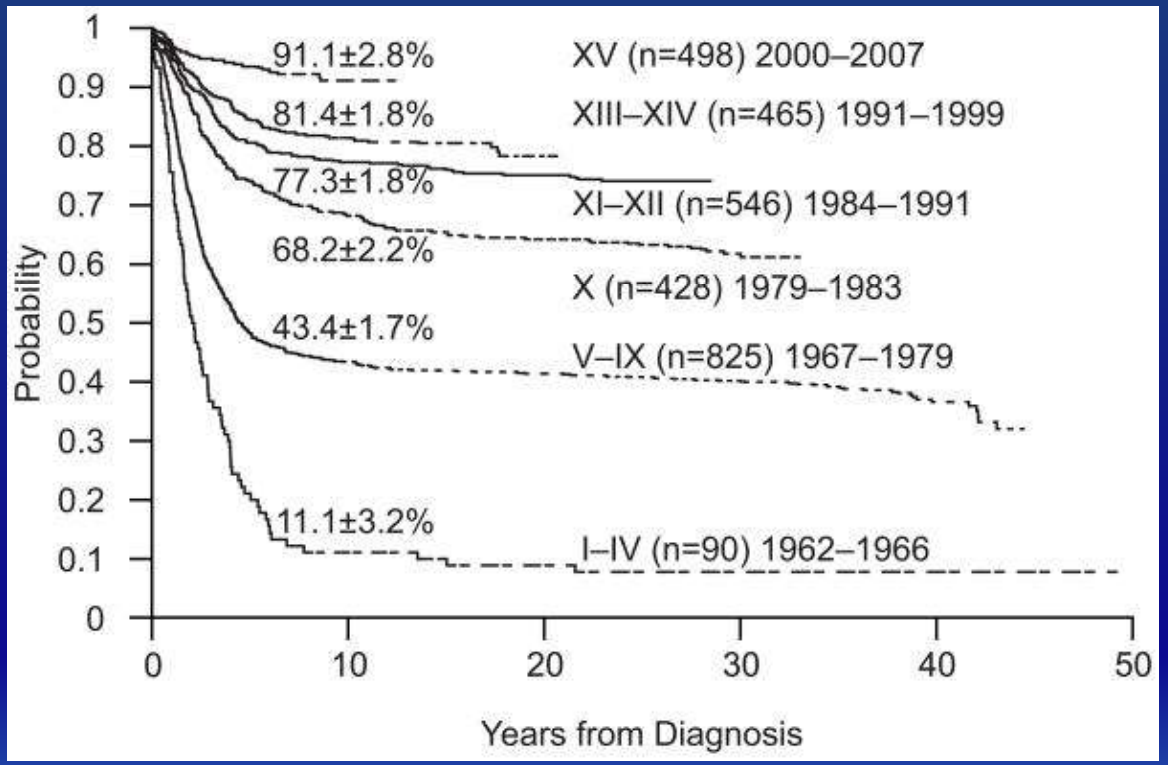
- The Children's Oncology Group (COG) is an international research organization, supported principally by the National Cancer Institute (NC I)
  - In the United States, 90-95 percent of all children under age 15 with a newly diagnosed malignancy are seen at a COG institution.
  - If a clinical trial is available, 50-60 percent of children eligible are enrolled.
  - For young children (less than 5 years of age) enrollment rates are much higher, 90 percent.
  - In 2007, the COG has over 70,000 children with cancer who were being managed with research protocols or were in active follow up.

Acute Lymphoblastic Leukemia ALL

- ALL is a type of caner in which the bone marrow makes too many immature lymphocytes.
- ALL is the most common type of childhood cancer with 3000 cases in the US per year.



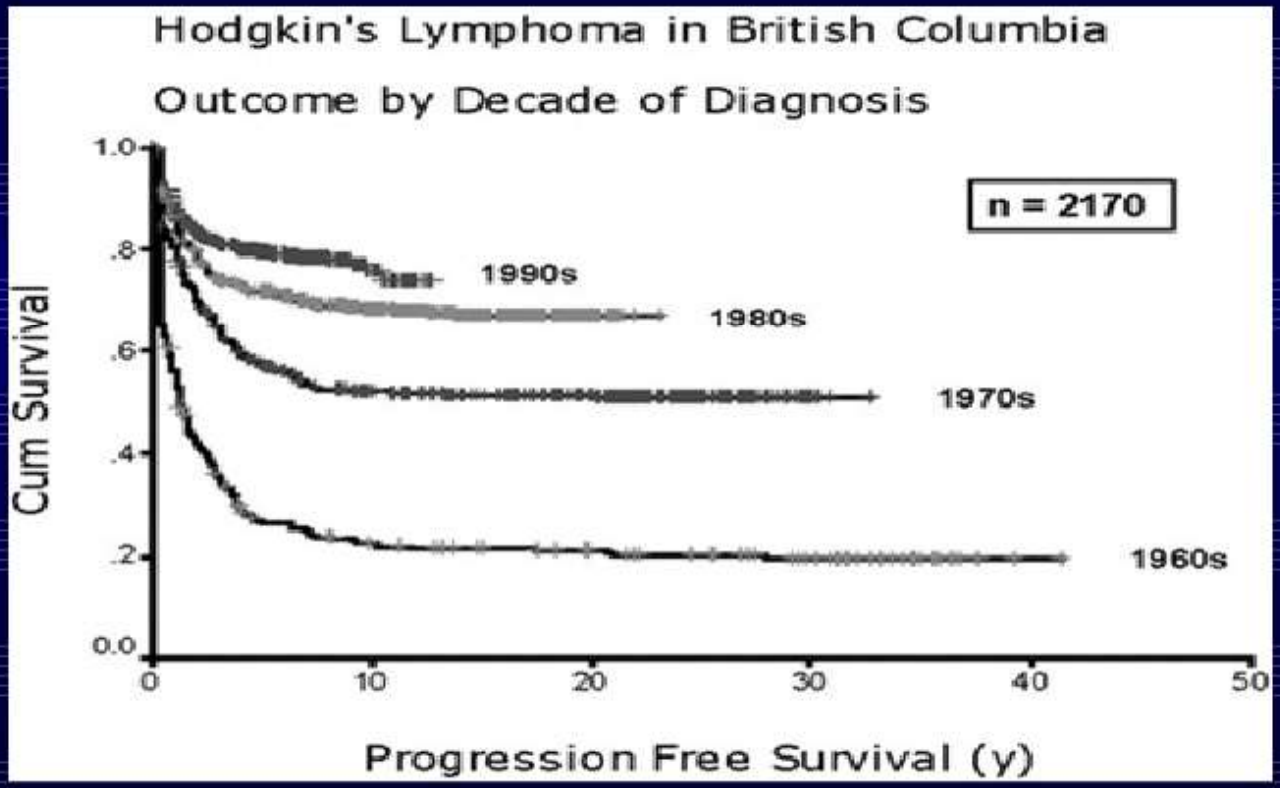
Survival Curves for Acute Lymphocytic Leukemia



Hodgkin Lymphoma

- 15 % of all Lymphomas
- First Diagnosed by Thomas Hodgkin in 1832
- Original survival at 5 years under 10%
- Improved Staging Techniques and Understanding of the pattern of spread helped direct management.
- Now curable in over 80 % of patients with cure rates climbing yearly.

Hodgkin's Lymphoma - Progress



The Future of Drug Development
Personalized Medicine Precision Medicine

- Personalized Medicine Tailoring health care to each persons genetic make up
  - The Right Drug
  - At the right dose for the right reason
  - To the Right Person
  - For the Right Reason

- Research shows that patients whose treatment was selected based on the molecular characteristics of their disease had significantly better outcomes.

Precision Medicine

- Precision medicine is a tailored approach to treatments for human diseases based on the characteristics of each individual.
- The number of FDA-approved molecularly targeted cancer therapies is approaching 100, and there are about 900 cancer drugs in development, mostly for adult cancers.
- In many cases, the abnormalities that cause pediatric cancers have similar counterparts in adult cancers. This makes it possible in some cases to redirect therapies that were developed for adult indications to pediatric uses