



FSMA Research Activities in FY2007

Jill Jarecki, Ph.D.
Research Director



2007 Research Update Session

- Jill Jarecki, PhD, FSMA Funded Research Activities
- Mark Gurney, PhD, deCODE, Quinazoline Project Update
- Tan Nguyen, MD, PhD, FDA, Orphan Product Development
- Arthur Burghes, PhD, OSU, Basic Research News
- Douglas Kerr, MD, PhD, Johns Hopkins University, Stem Cell Therapy for SMA
- Kathryn Swoboda, MD, University of Utah, Project Cure Update
- John Kissell, MD, OSU, VALIANT Clinical Trial for Ambulatory SMA Patients



Balancing Life's Tough Times™

FSMA Funded Research in FY2007

- Will fund \$4 million in research in FY2007
- 28 Basic Research Grants
- 2 Drug Discovery Projects
 - FSMA / deCODE Project
 - Quinazolines to increase SMN2 expression
 - Paratek Pharmaceuticals
 - Tetracyclines to correct SMN2 splicing
- Project Cure SMA Clinical Network
 - ~30 people funded. 7 sites
 - Phase II CARNI-VAL trial, completed November 2007
 - Adult ambulatory trial at OSU, starts July 2007
- Indiana Registry to facilitate clinical trial recruitment
 - Available fo use by any researcher or clinical trial network



FAMILIES OF SMA

Balancing Life's Tough Times™

The Pieces are Coming Together...

Biological Understanding
of SMA & Target Identification

Clinical Evaluation and
Protocol Development

Early Drug
Discovery Process

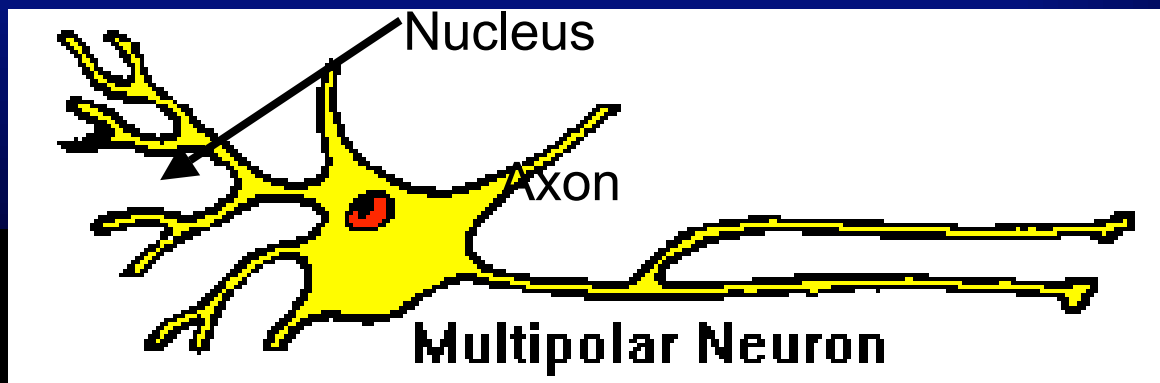
Alternate
Therapies

These approaches compliment each other and are
all essential to developing SMA treatments



Basic Research: Biological Basis of SMA

- In motor neurons SMN is found in complexes located in both the cell body and in the cell axons
- Why do low levels of SMN cause motor neurons to die?
 - Which SMN complex is critical? The axonal or the cytoplasmic/nuclear complex?
 - When can increasing SMN levels rescue SMA disease progression?
 - How is SMN expression controlled and regulated?
- What is the most effective route for making SMA drugs?
- Can we directly replace SMN?
- Can we directly replace lost motor neurons?



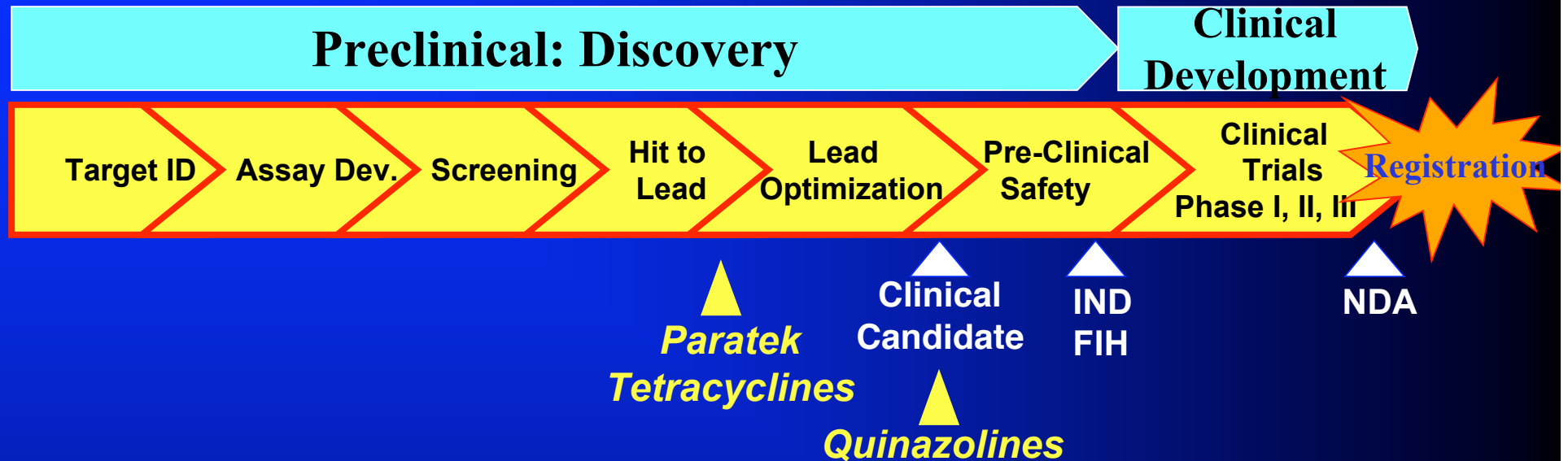
9 Newly Funded Basic Research Projects

- **Yukio Sasaki, Ph.D.**, Emory University, Dysfunction of Axon Guidance in Spinal Muscular Atrophy
- **Douglas A. Kerr M.D. / Ph.D.**, Johns Hopkins University, Transplantation of hESC-Derived Motor Neurons in Large Mammals
- **Matthew E. R. Butchbach, Ph.D.**, OSU, Mechanisms of Butyrate Neuroprotection in a Mouse Model of Spinal Muscular Atrophy
- **Charlotte J. Sumner, M.D.**, Johns Hopkins University, Targeting the Muscle and the Neuromuscular Junction for SMA Therapeutics
- **Hans Keirstead, Ph.D.**, UCI, Functional Characterization of High Purity Motoneuron Cultures Derived from hESCs.
- **Alex MacKenzie, M.D., Ph.D.**, Children's Hospital of Eastern Ontario, SMA cellular assay optimization and SMN2 inducing small molecule assessment.
- **Jean-Yves Masson, Ph.D.**, Laval University, DNA damage signaling and repair in Spinal Muscular Atrophy
- **Brunhilde Wirth, Ph.D., Eric Hahnen Ph.D.**, Klinikum der Universität zu Köln, Characterization of new drugs for SMA therapy*
- **Sibylle Jablonka, Ph.D.**, University of Wuerzburg, Analysis of cAMP Effects in a cell culture model of SMA*

*Co-funded with Initiative "Forschung und Therapie für SMA"

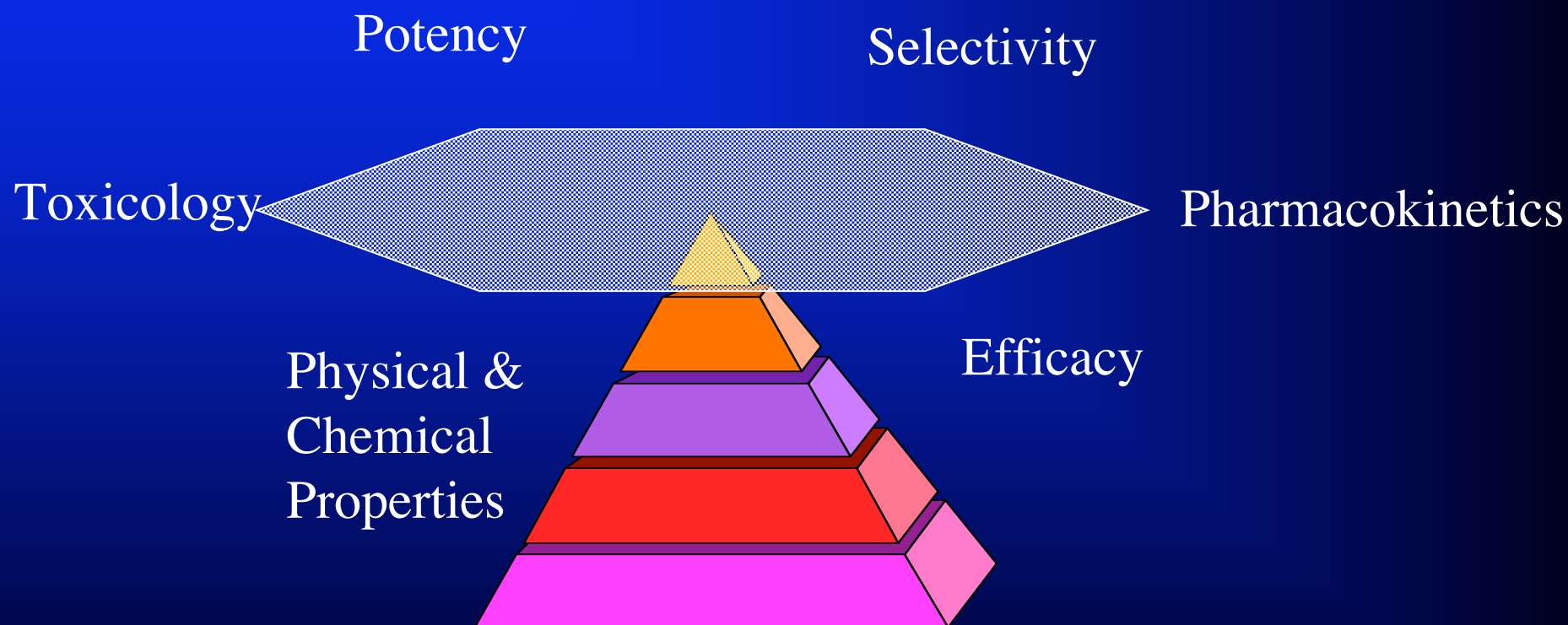


Drug Development Process



1. Compounds found in screening that increase SMN in cells are potential drug leads.
2. During lead optimization, chemical relatives of lead compounds are made.
3. Lead optimization is a reiterative process where compounds more effective than parental compounds are further modified until the greatest bioactivity obtained, toxicities and off-target activities reduced, and drug-like properties maximized.
4. Once a clinical candidate with desired specifications is found, an extensive series of preclinical safety studies are completed for an Investigational New Drug Application (IND) to the FDA.
5. If the IND accepted by the FDA, first-in-human (FIH) testing begins with safety studies, typically in healthy volunteers. This begins clinical development.

Lead Optimization Turns Compounds into Drugs: Finding the Correct Balance of All Required Properties in a Single Compound



Paratek Drug Discovery Program in Collaboration with CSHL

- Identified a tetracycline compound that directly corrects SMN2 splicing in vitro
 - Gems and SMN protein levels increased by several fold
 - Preliminary in vivo expression data from SMN2 transgenic mice presented in here by Michelle Hastings of CSHL and Joel Berniac of Paratek
 - Lead optimization and SAR determination are underway
 - New analogs synthesized at Paratek to generate more drug-like properties Currently working on increased BBB crossing
 - Screened for splicing activity at CSHL
 - Mechanism of action being assessed in the Krainer lab



deCODE / FSMA Project: Novel SMN Enhancing Drug

- Over 1000 2,4-diaminoquinazolines made & tested on SMN2 promoter assay in NSC-34 cells at deCODE
- Gem counts increased about 10-fold to carrier levels
- SMN promoter activity increased in spinal cord of mice as measured by β -gal levels
- Potent on the promoter assay (almost 200 compounds < than 50 nM)
- Oral bioavailability, efficient BBB crossing, metabolic stability, good carcinogenicity profile
- Increase survival on in SMA animal models by 20% to 30% as presented here by Dr. Matt Butchbach of OSU



Timeline for Quinazoline Project

- **Selected Clinical Candidate in May 2007**

- Potent on the promoter assay: $EC_{50} = 7 \text{ nM}$ ($n=22$); $EC_{90}=360 \text{ nM}$; ave.max promoter induction = $2.4x\uparrow$
 - Orally bioavailable with efficient BBB crossing: pharmacokinetics at 10 mg/kg p.o. ; rapid distribution into brain; $C_{\text{max}} = 1.1 \text{ }\mu\text{M}$; $t_{1/2} = 10 \text{ hr}$
 - MTD analysis shows no gross behavioral or physical effects after 8 days of dosing in mouse pups to 45 mg/kg and in adult rats to 70 mg/kg
 - Significant Increase in survival in animal model, improved motor function
- IND enabling safety studies to begin this month and will take 9 to 12 months to complete
 - Genotoxicity, General Toxicology, Safety Pharmacology (CNS, Cardiovascular, pulmonary)
 - Chemistry Manufacturing and Control data (cGMP production)



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Project Cure SMA

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deCODE

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