A BIOLOGIST'S INSIGHT INTO THE DEVELOPMENT OF NEW DRUGS AND MEDICAL DEVICES

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FR>EN translator

STORY OF *MYOREPAIR* & *SILKNEE*

- *MYOREPAIR*: a new biologic drug undergoing preclinical development
- The pharmaceutical company that discovered *MYOREPAIR* believes that it could help injured muscles heal faster

- *SILKNEE*: a new medical device undergoing preclinical development
- The orthopedics company that invented *SILKNEE* believes that it can replace damaged knee ligaments

STORY TOLD BY

- Joanne Archambault, PhD (Biology)
- 15 years of biomedical research experience
- Preclinical research work at Wyeth (now Pfizer)
  - Biologic drug now in Phase I clinical trials
- New product development group at Stryker
  - Novel orthopedic medical device did NOT go into human trials
- Translate French > English
  - French orthopedic companies
  - French orthopedic research journal
  - Pharmaceutical / biotechnology projects via agency clients

MYOREPAIR

New
Drug

MYOREPAIR

- *MYOREPAIR*: a new (protein) drug undergoing preclinical development
- Indication: help injured muscles heal faster
  - Use once per day until muscle is completely healed
- Prescribed by a doctor
- Will be delivered directly to injured muscle with device similar to insulin pen
- Target market: professional athletes with muscle injuries

PRECLINICAL DEVELOPMENT

- Manufacturing
- Formulation
- Sterility
- Stability
- Packaging
- Delivery device
- Antibodies
- Biomarkers

- Antibodies
  - Safety issue
  - Interferes with efficacy
- Biomarkers
  - Toxicity
  - Patient population
  - Predict efficacy

ANTIBODIES

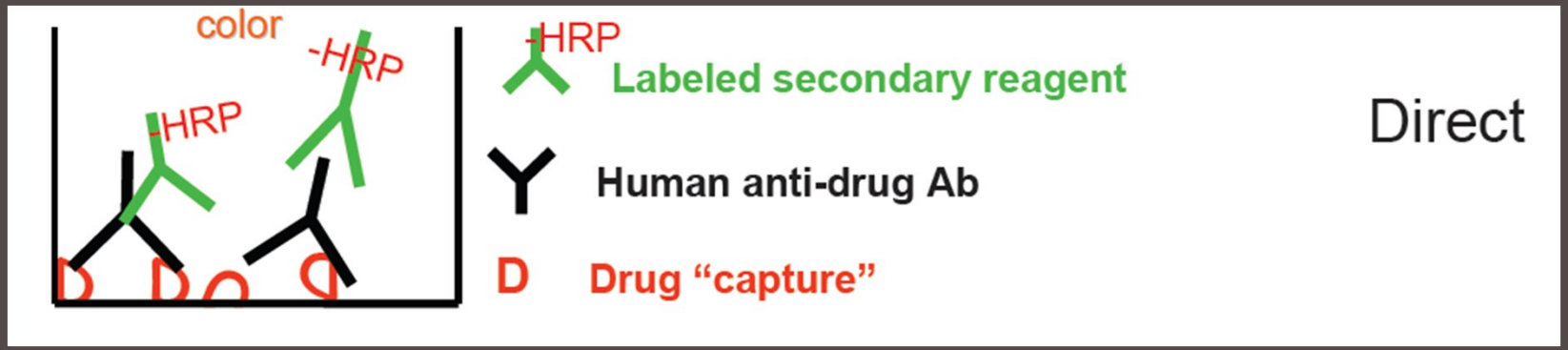
- WHAT – Molecule that binds to a foreign protein
  - Triggers immune response
  - Immunogenicity: unwanted immune response to drug
- WHY –
  - Causes side effects and reduces efficacy of drug
- WHERE – Blood, muscle tissue
- HOW – ELISA (enzyme-linked immunosorbent assay)
- WHEN – Preclinical testing, Phase I, II, III trials

IMMUNOGENICITY

- Regulatory guidance
  - EMA guidance on immunogenicity for biologicals
  - FDA Guidance for Immunogenicity Testing
- Measure anti-drug antibodies in patients treated with biologic drug (protein-based drug)
- Assays used to detect anti-drug antibodies
  - Look for binding antibodies
  - Look for neutralizing antibodies
- Develop during preclinical phase and validate during human clinical trials
  - Antibody response in humans generally cannot be predicted from animal studies!

ANTIBODIES TO *MYOREPAIR*

- ELISA format
  - Drug = *MYOREPAIR*
  - Test patient serum for anti-drug antibodies (Ab)
  - Compare to serum from same patient before he/she received the drug



  - Results may alter development plan

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BIOMARKERS

- WHAT – Indicator of physiological response to drug
- WHY –
  - Help to determine preclinical toxicity
  - Define population most likely to benefit from drug (safety)
  - Predict outcome of treatment (efficacy)
- WHERE – Blood, saliva, urine, muscle tissue
- HOW – ELISA, imaging, genomics, proteomics
- WHEN – Preclinical testing, Phase I, II, III trials

PRECLINICAL TOXICITY

- Preclinical animal testing required to determine toxicity of every new drug
- Biomarkers can extend testing beyond histopathology
- Assess blood cytokine, chemokine, and growth factor levels
  - Look for signs of toxicity and inflammation
- Evaluate differences between groups of animals
  - Vehicle-treated (control)
  - *MYOREPAIR*-treated

IMPROVE SAFETY

- Pharmacogenomics
  - How genetic differences in individuals affect the way people respond to drugs
- Get the right drug to the right patient
- Patient selection biomarkers
  - Predict response to molecular-targeted agents
  - Enrich trials with patients more likely to benefit and least likely to have side effects from drug

PREDICT EFFICACY

- Find marker(s) that can predict outcome FASTER than waiting for clinical end-point
- Approaches:
  - Genomics (transcriptional profiling)
  - Proteomics
  - Metabolomics
- Compare:
  - Normal muscle
  - Injured muscle
  - *MYOREPAIR*-treated normal muscle
  - *MYOREPAIR*-treated injured muscle

QUESTIONS?

SILKNEE

New
Medical
Device

SILKNEE

- *SILKNEE:* a new medical device undergoing preclinical development
- Indication: replacement of torn ACL (knee ligament)
- Made from silk that is braided into a small rope
- Available in different lengths
- Will be implanted by an orthopedic surgeon
- Target market: skiers with knee injury

PRECLINICAL DEVELOPMENT

- Product design
- Manufacturing
- Packaging
- Instrumentation
- Instructions for use
- Sterility
- Biocompatibility

- Sterility
  - ISO standards
  - Sterilization
  - Validation
- Biocompatibility
  - ISO standards
  - Type of material
  - Duration of exposure

STERILITY

- Sterile:
  - Free from viable micro-organisms
- Sterilization:
  - Validated process used to render product free from viable micro-organisms
- Types of sterilization:
  - Gamma radiation / E-beam radiation
  - Chemical – Ethylene Oxide
  - Moist heat (steam)
- Proper packaging needed to maintain sterility

ANSI/AAMI/ISO 11137

- Sterilization of health care products — Radiation
  - Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices
  - Part 2: Establishing the sterilization dose
  - Part 3: Guidance on dosimetric aspects

DEFINITIONS

- Bioburden:
  - Population of viable micro-organisms on product
  - Determined BEFORE sterilization
  - CFU: colony forming unit
- Sterility test:
  - Are viable micro-organisms present on product?
- SAL – sterility assurance level
  - Probability of having a viable micro-organism on product after sterilization
  - Surgically implanted devices → 10^{-6} SAL
  - Probability of 1 in 1,000,000 of finding non-sterile unit after sterilization

OVERVIEW - GAMMA STERILIZATION VALIDATION PROCESS

1) Product design
   - Device materials, packaging
2) Determine bioburden
   - Test 10 product items from three different production batches (total of 30 product items)
3) Determine verification dose
   - Reference tables in ANSI/AAMI/ISO 11137
   - Required radiation dose to apply to the product in KiloGrays (kGy) to achieve a specified SAL
4) Apply verification dose to product
   - Dosimeters used to monitor radiation dose applied

OVERVIEW - GAMMA STERILIZATION VALIDATION PROCESS

5) Test sterility
   - Confirm that all viable micro-organisms have been removed
6) Determine sterilization dose
   - Reference tables in ANSI/AAMI/ISO 11137
   - Choose sterilization dose to achieve desired SAL
7) Determine dose range
   - Large volume of products being sterilized
   - Range up to 2x sterilization dose
8) Dose mapping
   - Distribution of dose throughout irradiator
9) Routine processing / Dose audits

PRECLINICAL DEVELOPMENT

- Product design
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- Sterility
  - Sterilization
  - ISO standards
  - Assurance
- Biocompatibility
  - ISO standards
  - Type of material
  - Duration of exposure

WHAT IS BIOCOMPATIBILITY?

- Interaction between medical device and tissues/fluids of the patient treated with device
- One component of overall safety assessment for devices
- Biocompatibility of device depends on several factors
  - Chemical and physical nature of materials in the device
  - Types of patient tissue that will be exposed to the device
  - Duration of exposure
- Primary purpose is to ensure patient safety!

ISO 10993 – FDA*, EUROPE, ASIA

- ISO 10993 - Biological evaluation of medical devices
  - Part 1: Evaluation and testing in the risk management process
  - Part 2: Animal welfare requirements
  - Part 5: Tests for in vitro cytotoxicity
  - Part 6: Tests for local effects after implantation
  - Part 11: Tests for systemic toxicity
  - Part 12: Sample preparation and reference materials
  - Part 13: Identification and quantification of degradation products from polymeric medical devices
  - Part 18: Chemical characterization of materials

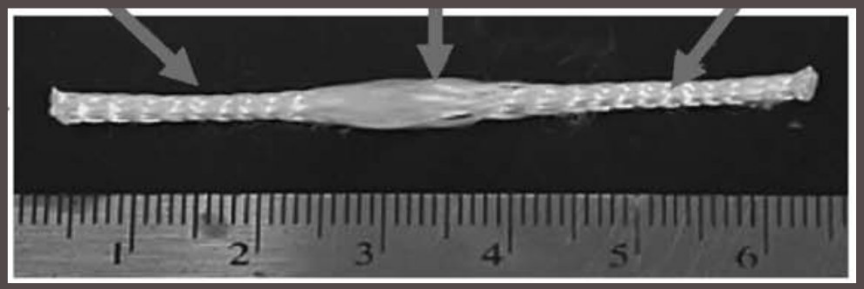
*FDA has additional requirements (USP <88>)

ISO 10993-1

Materials Biocompatibility Matrix

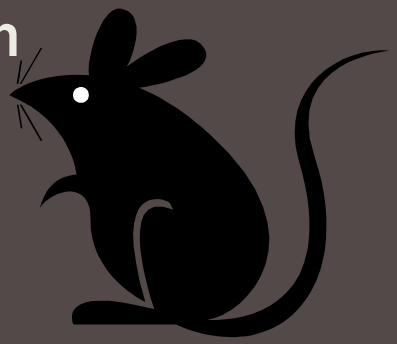
Device Categorized as:			Biological Effects									
Body Contact		Contact Duration Limited •Less than 24 hours Prolonged •24 hours to 30 days Permanent •Over 30 days	Cytotoxicity	Sensitization	Irritation or Intracutaneous Reactivity	Systemic Toxicity (acute)	Subacute and Subchronic Toxicity	Genotoxicity	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity
Implant device	Tissue/Bone	Limited	♦	♦	♦							
		Prolonged	♦	♦	♦	♦	♦	♦	♦			
		Permanent	♦	♦	♦	♦	♦	♦	♦			
	Blood	Limited	♦	♦	♦	♦	♦		♦	♦	♦	
		Prolonged	♦	♦	♦	♦	♦	♦	♦	♦	♦	
		Permanent	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦

TESTING IMPLANT BIOCOMPATIBILITY



- Implantation
  - Put directly in animal

- Systemic toxicity
- Skin irritation
- Sensitization



Inject <u>extract</u> of the implant

EXTRACTS

- Extraction vehicles:
  - Polar: 0.9% sodium chloride (saline)
  - Non-polar: vegetable oil
  - USP <88>: polyethylene glycol and alcohol in sodium chloride solution
- Extraction ratio (ISO 10993 Part 12)
  - Thickness > 1 mm: 25 cm^2 per 20 ml
- Incubate (heat, time, shaking)
- Inject into animal
- Compare with animals receiving extraction vehicle only

QUESTIONS?

STORY OF *MYOREPAIR* & *SILKNEE*

- *MYOREPAIR*: a new biologic drug undergoing preclinical development
- Based on the Stamulumab (MYO-029) drug that was being developed by Wyeth for muscular dystrophy in mid-2000s

- *SILKNEE*: a new medical device undergoing preclinical development
- Based on product by Serica Technologies (now owned by Allergan)

THE END

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