The Critical Path Institute (C-Path) is a non-profit organization set up to foster development of new evaluation tools to inform medical product development through responding to the needs of the Food and Drug Administration (FDA) Critical Path Initiative. C-Path’s Consortium:

- Act as a trusted, neutral third party working with industry, academia, non-profit groups and regulators
- Enable iterative EMA/FDA/PMDA participation in developing new methods to assess the safety and efficacy of medical products
- Seek regulatory endorsement of novel methodologies and drug development tools – biomarkers, clinical outcome assessments, models and in vitro tools.
- Develop and share data standards and databases.

The Predictive Safety Testing Consortium’s (PSTC) goal is to find improved safety testing methods over the and validate innovative safety testing methods under advisement of the FDA, EMA, and PMDA. PSTC utilizes a translational approach to qualify safety biomarkers in six working groups: kidney injury, liver injury, pancreatic injury, skeletal muscle, testicular toxicity, and vascular injury. Recently, PSTC qualified the first set of clinical safety biomarkers to detect drug-induced kidney injury.

The Duchenne Regulatory Science Consortium (D-RSC) develops tools to accelerate therapy development for Duchenne Muscular Dystrophy (DMD). D-RSC’s focus is on understanding natural history of the disease and disease progression [see poster X]. D-RSC has published a CDISC Therapeutic Area User Guide to describe database structure for Duchenne data, developed an integrated database of over 1,100 patients’ data and is working on developing a clinical trial enrichment platform for the disease.

**Skeletal Muscle Damage Biomarkers**

Biomarkers are used to monitor muscle injury and muscle health. Biomarkers include pro-inflammatory cytokines, tissue markers, and myosin isoforms. Myosin isoforms are a family of proteins that are involved in muscle function. They are expressed in different muscle fibers and can be used to assess muscle damage.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Tissue</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatine Kinase (CK)</td>
<td>Skeletal muscle</td>
<td>Highly abundant in skeletal muscle</td>
</tr>
<tr>
<td>Myoglobin (Mb)</td>
<td>Skeletal muscle</td>
<td>Component of myoglobin that is released from muscle injury</td>
</tr>
<tr>
<td>Troponin Type I (cTnI)</td>
<td>Heart muscle</td>
<td>Highly sensitive to heart muscle damage</td>
</tr>
<tr>
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</tr>
</tbody>
</table>

**Conclusion**

- Biomarkers are increased in DMD, and early DMD, but decrease over the course of DMD, probably reflecting remaining muscle function.
- Biomarkers may inform us on repair of muscle damage and for the type and location of damage in the muscle.
- Further work is needed to fully understand the dynamics in different diseases.

**Next Steps**

- PSTC is seeking qualification of this panel of biomarkers as clinical toxicity biomarkers.
- Further work is needed to establish a context of use in NMDs, but data is promising in some diseases.
- We are also looking to develop clinical grade assays for these biomarkers.

**Skeletal Muscle Damage Biomarkers**

- **CKM Biomarkers – rat muscle damage**
  - Performance based on 34 studies using 9 CKM toxins across multiple mechanisms of toxicity that result in the shared morphologic outcome of CKM degeneration/necrosis.
  - **Age:** No effect of age on the levels of the biomarkers.
  - **Gender:** The levels in females tend to be slightly lower than males (except FABP3 where it was higher).
  - **Ethnicity:** The levels were higher in African Americans relative to Caucasians.

**SKM Biomarkers in Muscular Dystrophies**

- **SKM Biomarkers are significantly upregulated in DMD, BMD, and LGMD2B**
  - Spatioli et al 2018 and Hathout et al 2015 both identified these proteins except MyoD as upregulated in DMD and to a lesser extent in BMD (FABP3 not up in BMD, GDF8 up similar amounts).

- **However, the biomarkers decrease over time, especially in older patients.** This may be due to loss of muscle tissue. To use these as biomarkers in dystrophies, we will need to see rapid large changes, or normalize to the amount of tissue remaining.

**SkM Biomarkers in SMA**

- **Significance of correlation of GDF-8 with MRI mass and motor function results in SMA type III patients.** T-Test of n=17 SMA type III patients.

**SkM Biomarkers in ALS**

- **S1T1 Levels Increased and GDF Decreased in Roche SMA Type III Observational Study after 1 year.**

**Letter of Support**

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