Novel biomarkers for Crohn’s disease drug development programs
Roadmap for biomarker qualification and precision medicine

Jiri Aubrecht PharmD, PhD
Treatment of Crohn’s disease

• Patient journey
  - Severe progressing disease vs mild disease

• Treatment options
  - Increased number of therapeutics
    • Traditional (salicylates, steroids, immunomodulators)
    • New generation (anti-TNF, anti-integrines, IL23p19, JAK)
    • Future (microbiome modulators, ....)
  - Efficacy ceiling

• Gap
  - Personalized/precision medicine approaches for clinical practice and drug development
    • “Right drug for right patient”
• Current status
  - Fecal Calprotectin (FCP) and C-reactive protein (CRP) are used in clinical practice and drug development
  - Research efforts in academia and industry
  - Pipeline of biomarkers

• Gaps
  - FCP and CRP are used in clinic and drug development, however not fully understood and not qualified as DDTs for CD
    • Large amounts of data available among institutions but not shared
  - Pipeline of biomarkers exists, however context of uses are not defined
  - No clear path to qualification
1. Establish collaborative project across academia and industry to enable qualification of biomarkers for CD
2. Identify gaps in Crohn’s disease drug development programs
3. Determine in what context a tool could be used to fill a gap within drug development program (COU)
4. Apply biomarkers to COU / Gaps
5. Biomarker Readiness Review
6. Redefine contexts of use based on biomarker readiness review
7. Align project with regulatory agencies

**Deliverables:**
1. An agreed upon hierarchical list of biomarkers to be pursued by the consortium to support unmet drug development needs in CD with input from stakeholders
2. Establishment of the project plan for the Crohn’s Disease Biomarker Consortium based on the strategic focus set out by the pre-Consortium
Defining biomarker COU categories

Disease Activity

• Biomarker approaches that will reduce need for endoscopies, stratify severity, determine active vs. remissive states.

Predictive/Prognostic & Treatment Options

• Biomarkers and/or sets of biomarkers to aid in predicting complications, response to therapies or determine courses of precision medicine.
Verification CD Biomarker Stratification & Pipeline

### Discovery
- CD64
- Neopterin
- Myeloperoxidase
- MMP–(1,2,3,8,9)
- Mannitol test
- IL13RA2
- I-FABP
- HMGB1
- Histidine & Tryptophan
- CXCL8
- COL3A1
- CCDC88B
- CAT

### Early Development
- NOD2/CARD 15
- I2
- FGF19
- ECM Fragments (Vim)
- Citrulline
- CBir1
- PredicSURE

### Late Development
- IL-6
- IL-22
- Fecal Lactoferrin
- pANCA
- ASCA
- OmpC
- TGF-α

### Ready for Regulatory Acceptance
- Fecal Calprotectin
- CRP

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**Biomarker Efforts**
- Landscape Analysis Publication
- CDBC

**Discovery**
- Biological Plausibility
- Characterization study
- Assay development
- Exploratory clinical studies

**Early Development**
- Analytical Assay Validation
- Specificity Studies
- Sensitivity Studies
- Correlator Studies
- Clinical Verification and exploratory work

**Late Development**
- Patient Level Data
- Clinical validation

**Ready for Regulatory Acceptance**
- Clinical validation

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**CDBC**
- Sufficient data to be compiled into regulatory submission

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Must verify what each biomarker has v. needs.
Final Contexts of Use for CD Biomarkers

• **COU**: (Fecal Calprotectin) as a biomarker that predicts long term remission, following induction therapy in patients in clinical trials with Crohn’s disease by quantifying the degree of inflammation as measured by ileocolonoscopy.

• **COU**: (Fecal Calprotectin) as an enrichment biomarker to stratify patients with Crohn’s disease at high risk for progressive increase in disease activity by assessing the degree of inflammation by ileocolonoscopy for inclusion in clinical trials.

• **COU**: (Fecal Calprotectin/ CRP) for use as a pharmacodynamic response biomarker able to identify probability when a patient with Crohn’s disease has achieved endoscopic response/ healing categorizing the patient as in remission in clinical trials.
## CRP

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## Fecal Calprotectin

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Continuing Activities

- **Complete Review of CD Regulatory Ready Biomarkers**
  - Fully outline biomarkers, COU, and data ready to be submitted to regulators in LOI

- **Define pre-LOI strategy**
  - Utilize the research and information gathered through regulatory ready review to initiate pre-LOI discussions with regulators

- **Pre-LOI discussions with regulators the strategy for biomarker approval**
  - Propose plan and put forth rational and receive feedback from regulatory bodies

- **Consortium formation**
  - With feedback from the regulatory body hone the plan for moving forward with biomarker approval.

**Timeline:**
- **July**
- **July - Aug**
- **Q4, 2019**
- **2020**
Next steps

• Establish consortium of stakeholders to qualify biomarkers as DDT for CD
• FCP and CRPO serves a blueprint for qualification of CD biomarkers
• Consortium will become partner of choice for others to qualify CD biomarkers