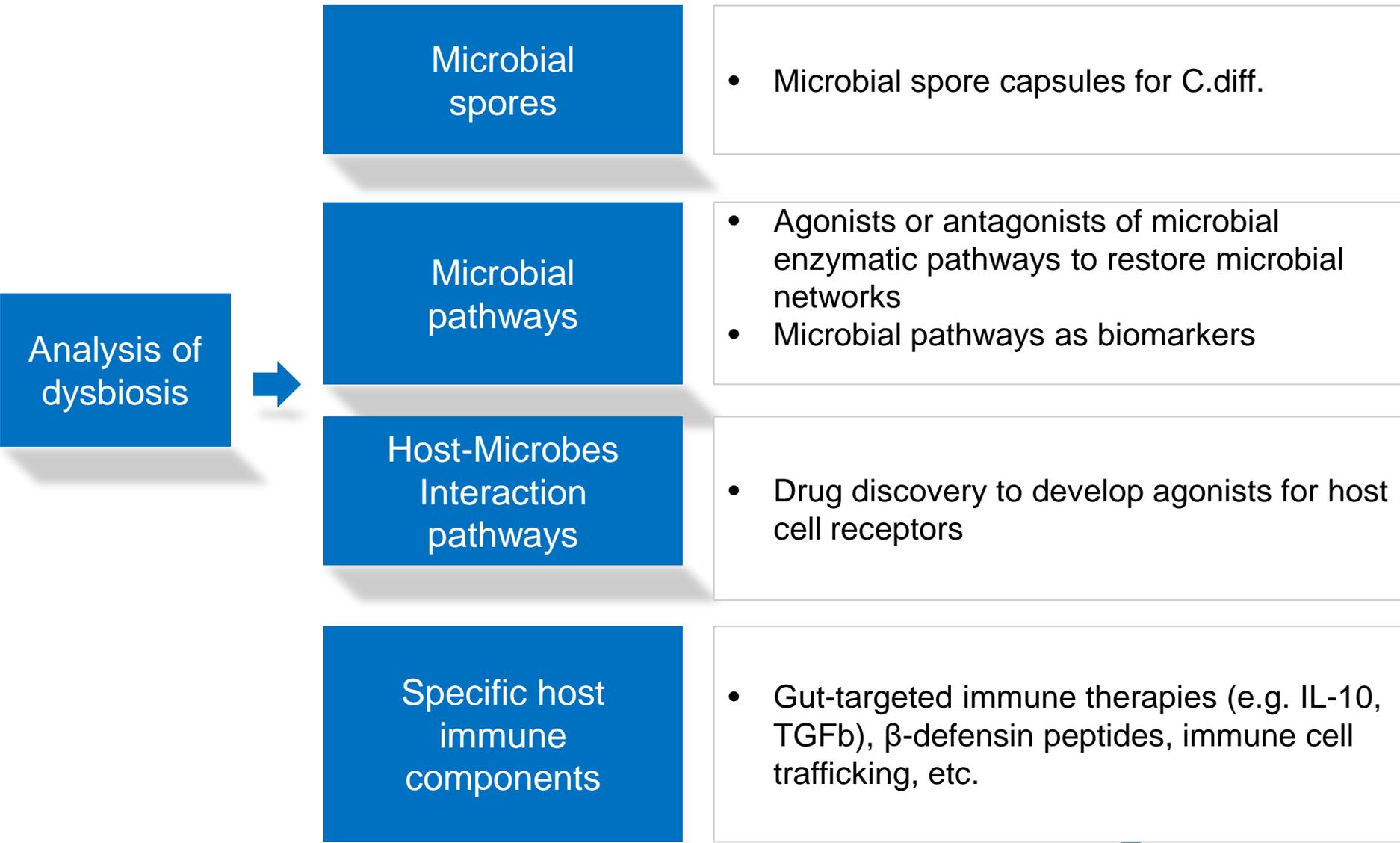# Approaches to Microbiome-Related Drug Discovery

Analysis of dysbiosis →

Microbial spores
- Microbial spore capsules for C.diff.

Microbial pathways
- Agonists or antagonists of microbial enzymatic pathways to restore microbial networks
- Microbial pathways as biomarkers

Host-Microbes Interaction pathways
- Drug discovery to develop agonists for host cell receptors

Specific host immune components
- Gut-targeted immune therapies (e.g. IL-10, TGFb), β-defensin peptides, immune cell trafficking, etc.

Strategic Approach to Leveraging of Microbiome-host Interactions

◆ **Prioritize focusing on 1) patient stratification approaches; 2) druggable microbial and host pathways involved in disbyoisis**

◆ **Deprioritize approaches focused on reconstitution of microbial ecologies**

   ◆ **Focus on opportunities to use microbiome to enhance IO therapy**

     – Data suggest opportunity for leveraging the microbiome to:

       1. Patient stratification for response

       2. Predict adverse effects to IO therapies– e.g. colitis

     – Further opportunity to enhance response to I-O therapy by identifying key druggable microbial pathways

     – Opportunity to expand into NASH. IBD space is encumbered for most companies

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Opportunities for Microbiome Impact in I-O

How could BMS leverage the microbiome information to improve I-O?

1. **Microbiome composition correlation with responders and non-responders**
    -   Work from Gajewski' and Zitvogel labs suggest path forward
    -   Issues to consider: will human complexity dilute microbiome impact? will different therapies have different "responder" microbiomes?

2. **Toxicity correlation with microbiome composition**
    -   Aalready compelling data with Ipi *(collaboration with Pamer/Wolchcok)*
    -   Issue to consider: will impact on toxicities be applicable across agents/combos?

3. **Identifying key targets or pathways to enhance immunotherapy**
    -   Less validation, but would be highly impactful.
    -   Issue to consider: Is the discovery platform based on screening of bacterial products capable of identifying pathways or targets that could be manipulated?

Diligence Findings: Key Takeaways

Enterome Strengths:

1. **Company focus on biomarkers and target discovery/validation, is aligned with strategic focus of BMS oncology**

2. **Significant experience in microbiome-based research including diagnostics**

3. **End-to-end solution for microbiome-based research**

4. **Collaborative mindset**

Challenges:

1. **No experience in establishing relationship between microbiome and response to IO therapies**

2. **Focus on only the gut microbiome for now**

4. **Clinical sample availability**

> Overall internal and external evaluations concluded that Enterome has the preferred technical approach to correlate microbial profiles to the efficacy and adverse events observed post IO therapies

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