**SPECFIC AIMS**

The gut microbiota consists of countless microbes including bacteria, virus and fungi. Studies utilizing gnotobiotic mice colonized with various bacterial communities have demonstrated that the bacteria which colonize the gastrointestinal tract aid in host nutrition, provide protection from invading pathogens, and enable the development of the immune system. However, the degree to which a gnotobiotic mouse’s immune system matures following conventionalization depends on the species from which the bacterial community originates, with mice conventionalized with mouse fecal communities developing significantly higher levels of CD4 and CD8 T-cells than mice colonized with human fecal communities.[1](#_ENREF_1) These finding suggest that there are signals that members of a specific species’ microbiota provide to their co-evolved host.

While the importance of species-specific interactions in the development of adaptive immunity has begun to be explored, it is currently unknown if the there are species-specific interactions at the level of the epithelium. Preliminary data from our lab suggests that there may be species-specific host-commensal interactions at the level of the epithelium as four days post colonization with either a mouse or human isolate of the same bacterial species leads to differential gene expression in the colonic epithelium. These data have lead to my **central hypothesis**that bacterial members of the gut microbiota are better suited to interact with their specific host’s epithelium than that of another host species*.* I will address my hypothesis by pursuing the following specific aims:

**Aim 1. Determine the functional and molecular response of enteroids in matched host-microbe interactions vs. mismatched host-microbe interactions.**

Our preliminary results suggest that a gnotobiotic mouse epithelium responds uniquely to a mouse bacterial isolate compared to a human isolate of the same species. Using mouse and human enteroids in combination with a bacterial strain collection that includes mouse and human derived isolates of the same species, I will assess changes in gene expression using microarrays. My working hypothesis is that patterns of epithelial gene expression will be conserved in matched host-microbe interactions when compared to mismatched host-microbe interactions.

**Aim 2. Determine if species-specific interactions enable preferential colonization by host-matched bacterial isolates.**

I will determine if species-specific selection of the microbiome is mediated by bacterial adaptation to a specific host environment. For this aim, I will perform competition experiments by injecting human or mouse enteroids with both mouse and human derived bacterial isolates. If bacterial members of the gut microbiota are better suited to interact with their host’s epithelium then I expect that the human derived bacterial isolates will colonize human enteroids better than mouse derived bacterial isolates and vice versa.

**Aim 3. Investigate if species-specific interactions are independent of TLR signaling.**

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| **Mechanism for Host Selection of bacterial communities** | **Example** | **Bacterial adaption** | **Addressed in Grant** |
| Host-microbe cross-feeding | Gut environment/metabolism favors one growth of one isolate | Preferential or more efficient usage of host or diet derived metabolites | Aim 2 |
| Immune selection | Produce antimicrobials that target specific groups of bacteria | Insensitivity/evasion of immune pressures | Aim 2/3 |
| Provide anchors | Prevent washout of desired bacterial groups | Express adhesion molecules that bind host receptors | Not testable in enteroid model |
|  |  | Produce products that favorably modulate host function | Aim 1 |

**Background and Significance**

1 Chung, H. *et al.* Gut immune maturation depends on colonization with a host-specific microbiota. *Cell* **149**, 1578-1593, doi:10.1016/j.cell.2012.04.037 (2012).