**Figure 1. Metagenome sequencing data profile and case filtering criteria.** **(a)** Left panel: micro-eukaryotic (red border) and bacterial (blue border) alignment count number in 9 cohorts, a total of 2,052 cases. Right panel: ratio of micro-eukaryotic and bacterial alignment counts number (purple border) in all samples **(b)** Microbiota rarefaction curve generated based on micro-eukaryotic chao1 diversity. **(c)** Case filtering criteria contained three primary sections, sample sequence quality control (nfiltered = 235), suspected contamination samples filtering (nfiltered = 192), and low-eukaryotic sequence depth samples discarding (nfiltered = 296). Excluding 723 cases, consistent with previous studies, approximately 30% of individuals were microeukaryotes free.

**Figure 2. Taxonomic distribution of enteric microeukaryotes and alteration of its alpha diversity across cohorts. (a)** Relative abundance of dominant enteric microeukaryotes phyla in healthy control, n=525 and CRCs, n=454. Ascomycota, Basidiomycota, Mucoromycota, Microsporidia, and Chytridiomycota were prevalent in both groups. **(b)** Relative abundance of dominant enteric microeukaryotes phyla in each cohort. **(c)** Compare the difference between healthy control and CRC. **(d)** Comparison of differences in chao1 index diversity indices between CRC (n = 454) and healthy control (n = 525) among the all and each.

**Figure 3. Meta-analysis identified a set of intestinal micro-eukaryotes strongly associated with CRC. (a)** Among 296 non-rare abundance candidates, the meta-analysis significant of micro-eukaryotes (n = 33, FDR < 0.01; n = 74, FDR < 0.1) derived from Mann-Whitney U test and adjusted the p-value with the conservative Bonferroni correction. **(b)** The main set (n = 74) performance across cohorts. The heatmaps revealed the two-sided Wilcoxon test and generalized fold change within individual studies. **(c)** The core set (n = 33) with pair fold change among all cohorts. And highlight the candidates whose fold change is larger than two times or less than a half. **(d)** Violin graph for the two outstanding performance micro-eukaryotes, A. rambellii and A. kawachii, in different studies.

**Figure 4. Meta-analysis of correlations among altered micro-eukaryotic and bacterial in CRC compared with the healthy control and adenoma. (a)** Left panel: correlation between the 33 selected micro-eukaryotes and 31 selected bacterial candidates in CRC samples. The pink diamond represented a significantly different paired correlation in CRC compared to healthy control, while the blue circle denoted the enormously different paired correlation in CRC compared to adenoma. Right panel: the top intra-micro-eukaryotic relationship in CRC. **(b)** Left panel: correlation between the 33 selected micro-eukaryotes and 31 selected bacterial candidates in the healthy control group. Right panel: the top intra-micro-eukaryotic relationship in healthy.

**Figure 5. Meta-analysis of comparison relationship between CRC and healthy control. (a)** Density graph with z-score of intra-bacterial, intra-micro-eukaryotic, and micro-eukaryotic-bacterial correlational comparisons. Left panel: the stacked density chart in all correlational comparisons. Right-top panel: the density plot for z-score of intra-bacteria. Right-middle: the density plot for z-score of intra- micro-eukaryotes. Right-bottom: the density plot for z-score of micro-eukaryotes-bacteria. **(b)** Definition of differential correlation classes. The front and back of the semicolon represent the characteristics of the relationship in CRC and the healthy control, respectively. **(c)** Percentage of differential correlational classes. Blue, orange, and yellow bar represented the intra-bacterial, intra-micro-eukaryotic, and micro-eukaryotic-bacterial groups, respectively. **(d)** Network for the differential correlation between CRC and control. Six clusters were automatically separated through the methodology affinity propagation cluster.

**Figure 6. CRC in vitro cell line validation. (TBA)**