Guardians of the gut: harnessing bioinformatics to study the gut microbiome and faecal microbiota transplantation in intestinal disorders

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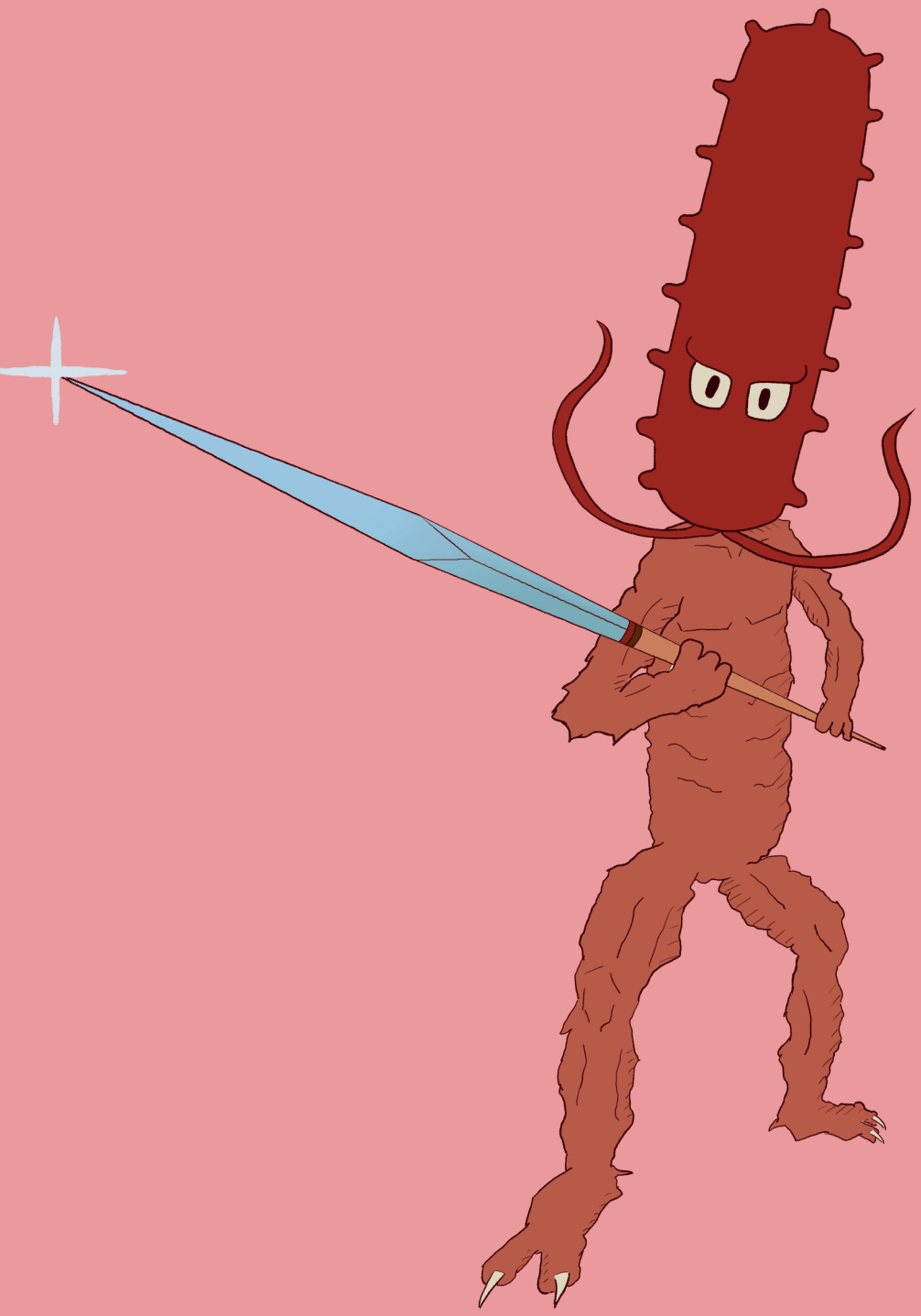

Chapter 2.2

Rational donor selection for fecal microbiota transplantation

Reply

Sam Nooij, Elisabeth M. Terveer, on behalf of the Netherlands Donor Feces Bank

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Dear editor,

We thank dr. Gianluca Ianiro et al. for the suggestion, in their reaction to our manuscript, to evaluate the donor microbiome for fecal microbiota transplantation (FMT) by carefully assessing donor history and analyzing the microbiome to predict a favorable microbial signature. We agree that studying successful donor-patient pairs is crucial in understanding complex microbiome-related disease pathology and subsequent cure. However, there are several arguments against the existence of a favorable microbial signature for recurrent *Clostridioides difficile* infections (rCDI) (1). For other diseases it is currently not yet reliable as predictor on an individual donor level.

Fecal suspensions from carefully screened donors without specific targeted microbiome screening for the treatment of patients with rCDI always show high (>80%) success rates world-wide. Still, the working mechanism of FMT to prevent recurrent CDI is not completely understood and immunological effects are probably involved in addition to restoring the colonization resistance by reintroducing a healthy microbiome. FMT seems to enhance *C. difficile*-specific cellular and antibody-mediated immunity, as it is associated with increased proportions of toxin B-specific T helper-17 cells as well as IgG and IgA antibodies specific for toxin A and B (2). Of note, the immunological effect that FMT can elicit may be of more relevance for other diseases, but is still difficult to predict. Interestingly, a study using FMT to promote response in immunotherapy-refractory melanoma patients revealed that of the two donors rationally selected based on a preferred microbiota profile, only one was associated with tumor suppression in the patients (3). Nevertheless, donor selection is gaining ground despite the lack of knowledge about a preferred microbial signature to define a super donor on the individual donor level. A large FMT center in China has performed over 60,000 FMTs across more than 5,000 patients for various gastrointestinal diseases (recurrent CDI, inflammatory bowel disease, irritable bowel syndrome) and extraintestinal diseases (autism spectrum disorder and Parkinson's disease) (4). Our Chinese colleagues developed a very stringent donor screening program including 16S rRNA gene amplicon sequencing of stool samples to evaluate bacterial compositions. These data would provide a unique opportunity to evaluate the efficacy of FMT from various donors, (serious) adverse events and long-term follow-up of patients.

Our Italian colleagues mention that engraftment of donor microbiota is low after a single fecal infusion and disappears gradually over time after FMT. However, Goloshchapov et al. found significant long-term changes of the gut microbiota of healthy people one year after FMT, accompanied with transient changes of systemic immune parameters (5). Similarly, the study of Varun Aggarwala et al. found stable engraftment of 71% of donor microbiota strains in recipients up to 5 years post-FMT (6). Nonetheless, it remains unknown whether long-term bacterial engraftment is important for clinical success, and of clinical significance. Notably, engraftment was not correlated to the clinical success

in studies of five different FMT-treated illnesses (rCDI, ulcerative colitis, Crohn's disease, metabolic syndrome, infection with extended-spectrum betalactamase producing bacteria) (7). In addition, the statement that the identification of specific donor microbiome signatures before FMT can predict outcome, neglects the importance of the recipient microbiota. This was clearly demonstrated by Schmidt and colleagues in a recent meta-analysis of 142 FMTs that showed that recipient factors consistently outweighed donor factors in driving FMT outcomes (7). Besides, it remains difficult to define a 'healthy' microbiome without a thorough understanding of all its constituents, including also Archaea, viruses and fungi and their function in the gut ecosystem.

Long-term adverse events definitively related to FMT have not been reported and seem rare (8), but long-term follow-up with microbiome analyses, immunological parameters and clinical data is needed to recognize persistent engraftment and late adverse events. This is of particular importance for younger patient populations with non-CDI FMT-treated disorders. A recently completed survey in Europe demonstrated that of 31 FMT centers from 17 countries, 42% of all FMTs were administered for experimental indications other than rCDI (9). This illustrates the urgent need for an international registry to collect information from both donors and FMT-treated patients with follow-up of at least 10 years, and storage of stool samples from patients and donors by FMT centers. Such a registry is active in the US (American Gastroenterological Association) and is currently initiated in Europe by the European Working Group. We think this is an essential next step in both rationalized donor selection and establishing the safety of FMT also on the long term and enables action on previously unforeseen potential adverse events.

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