Cannabinoids and the Microbiome:

How the Tone Impacts Clinical Trial Strategy

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• The circadian clock regulates the eCB system and the gut microbiota
  ➢ Human and animal studies

• Cross-talk between the eCB system and the gut microbiota
  ➢ Most studies are in animal models

• Aging affects circadian rhythm, the eCB system and the gut microbiota
  ➢ Human and animal studies

• Cannabinoids may be beneficial for gut health
  ➢ Emerging area in clinical trials

*What factors do we need to consider as we start to conduct cannabis clinical trials in the GI space?*
The Endocannabinoid (eCB) System

- Identified in 1990s
- Two receptors (CB1 and CB2) and their ligands (2-AG and AEA) have been identified
- Phytocannabinoids (THC and CBD) act on the CB1 and CB2 receptors
- The eCB system regulates many processes, including inflammation, immunity and metabolism
- Endocannabinoid tone: expression and activity of the eCB system components

Cannabinoid receptors are distributed widely in the GI tract

- CB1 is expressed in neurons, endocrine and epithelial cells
- CB2 is expressed in neurons and immune cells
- CB receptor activation is associated with reduced gut motility, reduced inflammation and increased permeability
- Polymorphisms in eCB system genes are associated with inflammatory bowel syndrome (Ambrose and Simmons 2019 *Journal of Crohn's and Colitis*, 2019, 525–535)
Gut Microbiota

- More than 1 trillion organisms
- The host and the inhabiting organisms = “superorganism”
- Immune and metabolic functions
- Maintenance of intestinal epithelium integrity
- Composition varies in individuals and can change depending on diet, age and health status
- A high F/B ratio is associated with obesity

Source: Rinninella et al. 2019 Microorganisms 7(14)
eCB System/Gut Microbiome Cross-Talk

- eCB system is overactivated in conditions of microbiome dysbiosis
  - Increased gut permeability and release of bacterially-derived LPS into the circulation
  - Increased eCB tone in adipose tissue leading to increased fat mass
  - Feedback to the gut further increasing permeability and leading to a vicious cycle

- THC administration prevented the high-fat diet-induced increase in the Firmicutes:Bacteroidetes ratio (Cluny et al. 2015. PLoS ONE 10(12): e0144270)

The Circadian Clock

- Adaptation to the 24-h light/dark cycle
- Controls feeding behavior, body temperature, sleep-wakefulness, hormone secretion and metabolism
- The master clock is in the suprachiasmatic nucleus (SCN) in the hypothalamus
- There are peripheral clocks in most organs, which control their function and feedback to the master clock
- The gut clock regulates multiple functions, including nutrient absorption and colonic motility

Source: Liang X and G FitzGerald 2017 J Biol Rhythms 32(6) 505–515
Circadian Rhythm: *The Endocannabinoid System*

- 2-AG levels are low at night and increase during the day
- AEA levels are low in the evening, peak in the morning and decrease during the day
- Sleep deprivation affects AEA levels
Circadian Rhythm: The Gut Microbiome

Source: Liang X and G FitzGerald 2017 J Biol Rhythms 32(6) 505–515
Aging: Circadian Rhythm, eCB System and the Gut Microbiome

- eCB tone decreases as we age
- Aging is associated with disrupted sleep patterns and reduced ability to maintain core body temperature
  - Low dose cannabinoids may be effective in restoring circadian rhythm and thermoregulation

- The composition of the gut microbiota changes with age
  - There is an enrichment of health-associated bacteria in very old individuals

Source: Hodges E & N Ashpole. 2019 Neurobiology of Aging 79:110e118

Source: Biagi et al. 2016 Current Biology 26, 1480–1485
Clinical Trial Strategy: Opportunities and Challenges

- Healthy population recruitment
- Study design
- Outcomes

Other Disease-Related: 25%
Seizures: 22%
Cancer-Related: 15%
Other Disease-Related: 11%
Psychosis: 10%
GI: 3%
Substance Abuse: 6%
Pain: 6%
Anxiety: 2%
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Source: www.clinicaltrials.gov
Clinical Trial Strategy: Recruitment

- Participant health status and age
- Participant lifestyle
  - Sleep habits
  - Diet
- Participant genetic profiles
  - SNPs in eCB system genes are associated with IBD (Ambrose and Simmons 2019 Journal of Crohn's and Colitis, 2019, 525–535)
What is a Healthy Population?  *KGK Survey* (48 Respondents)

1. In general, how would you rate your own health?
2. Do you eat a balanced diet?
3. How many scheduled meals do you eat in a day?
4. Do you eat these meals at the same times each day?
5. Do you have a regular sleep schedule?
6. How much sleep do you get per night?
7. Do you wake up feeling well-rested?
8. How many bowel movements do you have per day?
9. When do you usually have your bowel movement(s)?

![Self-Reported Health Status Pie Chart]

- **Excellent**: 13%
- **Very Good**: 50%
- **Good**: 29%
- **Fair**: 8%
- **Self-Reported Health Status**

13% Good, 50% Very Good, 29% Excellent, 8% Fair.
Clinical Trial Strategy: Recruitment

• Only 36% of our respondents who reported that they were in good, very good, or excellent health had a balanced diet, a regular sleep pattern, and regular bowel movements.
Clinical Trial Strategy:

Study Design

• Run-in period
  ➢ Ensure all participants have similar dietary and sleeping habits prior to the study
  ➢ Account for large placebo effect, which is often observed with GI studies

• Time and length of study visits

• Time of investigational product administration

• eCB tone of participants (circulating levels of 2-AG and AEA)

Outcomes for GI Health Studies

• Microbiome screening of individuals via fecal collection and subsequent extraction of RNA/DNA sequences

• Gastric emptying (via radiopaque markers), gas concentration (intestinal gas capsules) and/or GI inflammation (fecal calprotectin or lactoferrine)

• Validated gut-health questionnaires (bowel habits, GI symptoms, and quality of life)
Conclusions

• The cross-talk between the eCB system and the gut microbiota is an emerging field

• eCB tone should be considered in clinical trial design

• Cannabinoids may be beneficial for gut health
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