Study design of a single-center, open-label, three-period, fixed sequence phase 1 study of **cannabidiol and tacrolimus**

SCHOOL OF MEDICINE
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Background

A case study demonstrated a potential pharmacokinetic drug-drug interaction between cannabidiol and tacrolimus.[1] Our clinical trial dedicates to investigating the interactions cannabidiol (CBD) and tacrolimus (Tac). ClinicalTrials.gov: NCT05490511

Tacrolimus

- Tacrolimus is a staple immunosuppressant to prevent graft rejection for transplant recipients through blocking interleukin-2 (IL-2) transcription.
- Outside of its narrow therapeutic window can cause graft rejection or nephrotoxicity.
- It is **metabolized by CYP3A4/5**. CYP3A5 polymorphism contributes up to 45% inter-individual variability.[2]

Cannabidiol

- Cannabidiol was reported to **inhibit CYP3A5** 7-fold stronger than CYP3A4 *in vitro*.[3]
- In addition, cannabidiol has **immunosuppressive properties**. However, the mechanism remains unclear.

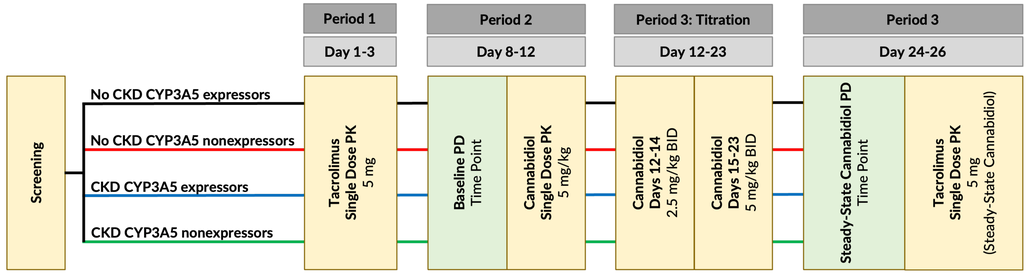
Hypotheses

- **Pharmacokinetics**: $AUCR_{0-\infty}$ of Tac with CBD to Tac alone will be increased in CYP3A5 expressors (*1 allele carriers) to a greater extent than in CYP3A5 non-expressors.
- **Pharmacodynamics**: CBD will induce regulatory T cells (Tregs) causing immunosuppression that may add to that of Tac.

Trial Initial Results: See Poster LB-009
In Vitro Experiment: See Poster PT-027

Cell culture schema

Study Design



- **Inclusion criteria**: Adults aged 18-65
- **Exclusion criteria**: CYP3A4*22/*22 carrier, positive urine test for cannabinoids, liver impairment, and end-stage renal disease
- **Stratification** based on CYP3A5 genotype and chronic kidney disease (CKD) status

Primary Outcome [Pharmacokinetics]

- **$AUCR_{0-\infty}$** of Tac with CBD to Tac alone between CYP3A5 expressors and non-expressors
- Each period has 10 blood draws, follow-up visits are up to 48 hours for tacrolimus and 96 hours for cannabidiol

Secondary Outcomes [Pharmacodynamics]

- Degree suppression of lymphocyte proliferation (cell proliferation assay)
- Lymphocyte population distribution and differential gene expression (single-cell RNA sequencing)

Six conditions to undergo cell proliferation assay and single-cell RNA sequencing

Time Point	Condition	*Ex Vivo* Treatment	Cannabidiol Plasma Concentration
Period 1	1	No treatment	None
	2	CD3/28	None
	3	CD3/28 & tacrolimus	None
Period 3	4	No treatment	Steady-state concentration
	5	CD3/28	Steady-state concentration
	6	CD3/28 & tacrolimus	Steady-state concentration

CD3/28, anti-CD3/28 antibody for T lymphocyte stimulation

Result

Enrollment status (as of 3/7/2024)

Study Status	Subjects Screened
Completed	21
Ongoing	2
Scheduled to start	3
Withdrawn	
Due to adverse event	1
Due to scheduling conflict	1
Prior to start	6
Ineligible	4
Total	38

Baseline characteristics of subjects who have received ≥1 dose (as of 3/7/2024)

Subject Characteristics	All Subjects (n=23)
Age, yr	41.1 ± 16.6
Sex	
Male	6 (26.1%)
Female	17 (73.9%)
BMI, kg/m²	27.3 ± 4.6
Race	
White	14 (60.9%)
Black	7 (11.5%)
Asian	2 (8.7%)
Ethnicity	
Hispanic	1 (4.3%)
Non-Hispanic	22 (95.7%)
Hct, %	39.3 ± 4.1
Albumin, g/dL	4.3 ± 0.3
SCr, mg/dL	0.9 ± 0.3
eGFR, mg/mL/1.73 m²	95.3 ± 18.8
> 60 mg/mL/1.73 m²	21 (91.3 %)
< 60 mg/mL/1.73 m²	2 (8.7 %)

References: [1]Leino AD, et al. (2019). *Am J Transplant* **19**(10):2944-2948. [2]Haufroid V, et al. (2004). *Pharmacogenetics* **14**(3):147-154. [3]Yamaori S, et al. (2011). *Life Sci* **88**(15-16):730-736.