Executive Summary

Cannabis abuse in Hong Kong has been increasingly popular among drug abusers. Currently, most evidence on neurocognitive impairments resulted from cannabis use are mainly from cross-sectional studies. There is also a lack of study on any common genetic vulnerability of cannabis use disorder (CUD) and its associated neurocognitive functioning among cannabis users, in particular in the Asian population.

"Substance misuse To Psychiatric disorders for Cannabis—Prospective evaluation on Cognitive function and its associated Genetic vulnerability in cannabis users" (SToP-C—PeCoG) study here aimed to examine the temporal changes in neurocognitive functions from cannabis use, and whether genetic vulnerability might correlate with addiction to cannabis/ CUD and the related changes in neurocognitive outcomes, focusing on global cognition, frontal executive function and memory functions.

This study employed a prospective, naturalistic, non-interventional longitudinal design that followed up individuals who abused cannabis over an 18-month period. Participants were recruited via community outreach, from the Counselling Centres for Psychotropic Substance Abusers, substance abuse clinics operated under Hospital Authority, and by self-referrals to the research team. Consented participants were assessed at baseline and every three months on various outcomes, including their level of cannabis dependence, severity of CUD, global cognitive function, frontal executive function and memory functions using the Severity of Dependence Scale (SDS), Structured Clinical Interview for DSM-5 Disorders–Clinician Version (SCID-5-CV), Montreal Cognitive Assessment (MoCA), Frontal Assessment Battery (FAB) and Wechsler Memory Scale 3rd edition

(WMS-III), respectively. Genomic analysis was also performed using venous blood samples from the consented participants over a predefined panel of SNPs selected *a priori* based on GWAS and candidate-gene studies relevant to CUD and neurocognitive function or disorders.

One hundred and nine participants consented and completed the baseline assessment. Ninety participants (82.57%) constituted the follow-up sample and genome-association analysis. The mean age of the participants was 28.86 years (SD = 9.65) and the majority were male (58.89%), with an average of 12.25 years of formal education (SD = 2.63). They were suffering from DSM-5 defined CUD with moderate severity (M = 3.81, SD = 2.85) and were psychologically dependent on cannabis (M = 4.07, SD = 3.48). Among demographics, including age, gender, years of education, and lifetime duration of cannabis use, only years of formal education appeared to be the most consistent and significant factor positively influencing all three tested neurocognitive functions (B's = 0.23 – 3.94; all p's <0.001). Participants with higher educational levels tended to show preserved neurocognitive functioning in MoCA, FAB and all domains of WMS-III in this study. Global cognitive function and frontal executive function from cannabis use remained in the respective normative range within the whole study period, but working memory impairment was noted (Means: 93.89 – 99.54). Recent cannabis use was the most significant predictive factor on the negative impact on immediate memory (B = -0.82) and general memory (B = -0.59) associated with cannabis use over time. Two cannabis use-related SNPs, rs80030908 on chromosome 13 and rs73229090 on chromosome 8, identified from this study showed preliminary associations with the baseline frontal executive function and general memory, respectively, but did not predict the severity of CUD nor the longitudinal trajectories of the neurocognitive functions associated with cannabis use.

In conclusion, the current 18-month study showed that despite the global cognitive function and executive function might be relatively preserved in adult cannabis users, cannabis use did have

significant impact on different aspects of memory functions, with working memory being the most negatively impacted. Educational level and recency of cannabis use were the two most significant factors predicting the detrimental effects on neurocognitive functions associated with cannabis use. The two SNPs, rs80030908 on chromosome 13 and rs73229090 on chromosome 8, identified from this study are still far from conclusive to be used as biomarkers for predicting the trajectory of neurocognitive changes from cannabis use. Clinicians and professionals working in the anti-drug fields should continue educating the public about the "Not Now. Not Ever" principle towards cannabis, especially targeting the evidence-based negative impacts on neurocognitive functions from cannabis use as researched in this study and the existing literature. Vulnerable cannabis users, in particular those with low educational level should have their cognitive functions carefully monitored. Cannabis users and the general public should also be warned about the harms on memory functioning from the recency (acute) effect of cannabis use ("Not Now"). With the extensive literature supporting abstinence on improvements in cognition, long-term abstinence from cannabis use should still be strongly encouraged ("Not Ever").