## Q&A

### 1. 治療 HIV 感染的未滿足需求是什麼？

### What are the unmet needs in HIV treatment?

目前市場上有 30 多種抗逆轉錄病毒藥物(ART); 然而 HIV 感染仍無法被治癒。ART 藥物無法根除 HIV 病患體內病毒，主要原因在於病患體內持續存在的 HIV 病毒庫(reservoir)，故只要停止使用 ART，已被壓制到極低含量的病毒會立即反彈。 目前，HIV 感染病患必須每天服用具多種抗病毒機轉的組合式藥物以維持病毒處在受抑制狀態。HIV 感染治療未滿足的需求包含病患需要終生服藥、長期毒性以及汙名化。此外，病患的低服藥順從性可能會導致病毒突變進而對藥物產生抗藥性，因此，較低頻給藥頻次較低的注射劑型 HIV 藥物已逐漸變成現在的治療趨勢。無 ART 藥物仍可維持病毒量不反彈的新治療選擇仍持續被探索與研究，例如功能性治癒 HIV。

There are more than 30 antiretroviral (ART) drugs available in the market; yet the disease is far from being cured. ART alone cannot eradicate HIV due to the persistence of viral reservoirs and the disease can rebound following discontinuation of ART. Currently, patients infected with HIV need to take a combination of ART daily to keep the virus suppressed. The

burden for patients of taking pills every day for life time and the unappreciated long-term toxicity and stigma are the unmet needs. In addition, patient' s low compliance in such a daily regimen could induce viral mutation and become resistant to the treatment and as such, there is a trend to move into less frequently administered injectable HIV drugs. New treatment options with novel mechanisms of action should be explored in order to achieve ART-free virologic remission, i.e., a functional cure.

## 2. UB-421 是什麼?其作用機制又為何？

### What is UB-421 and its mechanisms of action?

UB-421 是一株 Fc-無糖基(Fc-aglycosylated)、不會耗竭 T 細胞(non-T cell depleting)、和 CD4 專一性 (CD4 -specific)的擬人化 IgG1 抗體，它源自於一株名為 B4 的鼠源單株抗體。UB-421 的結合位點為 HIV-受體複合物上的不連續的構象表位 (conformational epitopes)，包括 CD4(domain 1)。 基本上，UB-421 是一個與 HIV 競爭 CD4 結合位點，進而阻止 HIV 進入 T 細胞的抗體。藉由此作用機轉，HIV 病毒包含抗藥性病毒株皆可有效被 UB-421 抑制。在臨床試驗中，重複施打 UB-421 展現出極佳的病毒抑制活性。 此外，UB-421 還具有增強免疫系統的活性，這項特性對 HIV 和癌症治療具有重要醫療意義。

UB-421 is an Fc-aglycosylated, non-T cell depleting and CD4-specific humanized IgG1 antibody derived from the parent murine antibody B4, which binds to discontinuous, conformational epitopes on the HIV-receptor complex, including CD4 (domain 1). Basically, UB-421 is an antibody that binds with competition edge to the site where all HIV variants attach, blocking their entry into the host cell and preventing the virus' activity. By doing so, essentially all HIV variants including resistant

viral mutants are highly sensitive to inhibition by UB-421.

In clinical trials, repeat-dose UB-421 exhibited remarkable high viral suppressing activities that are unprecedented.

UB-421 has additional immunomodulatory activity bolstering the immune system which has implications in HIV and cancer treatments.

3. 請說明 UBP 的技術，它與目前可用的 HIV 感染治療不同之處在哪？

Explain UBP’ s technology. What makes it different from currently available treatments?

目前可用於 HIV 感染患者的普遍治療方法是抗逆轉錄病毒療法 (Anti-retroviral Therapy，ART)。雖然 ART 可以大幅減少 HIV 病毒的傳播，但並不能治癒 HIV 感染。此療法需要每天服用多達 6 種具不同作用機轉的抗 HIV 藥物，且須終生服用不能中斷。如果病患錯過劑量或有一段時間未服用藥物，體內的 HIV 載量極容易反彈，且可能會產生抗藥病毒株。 UBP 正在開發一種治療 HIV 感染的創新單株抗體 UB-421，該抗體可抑制 HIV 病毒進入 T 細胞，從而阻止 HIV 的繁殖。我們的抗體獨特之處在於它與 HIV 競爭位於 T 細胞上的 CD4 結合位點，進而阻止 HIV 進入 T 細胞，且可在不產生抗藥性的情況下阻止病毒活動。因此，甚至可以用 UB-421 治療產生抗藥性的 HIV 感染。 在臨床前研究證明 UB-421 抗體可阻止 HIV 的傳播後，我們接續在 1 期，2a 期和 2 期人體臨床試驗中對 UB-421 進行研究。在 2 期臨床試驗中，我們發現 UB-421 可有效抑制 HIV 病毒量長達 2-4 個月。此外，我們也觀察到 UB-421 可以增強患者的免疫系統活性，而該特性顯示 UB-421 具有成為功能性治癒 HIV 感染藥物的優良潛力。

The common treatment currently available for patients with HIV is virus-targeting antiretroviral therapy (ART). While ART can minimize the viruses spread, it is not a cure. It also requires a cocktail of up to 6 different classes of drugs that must be taken daily for the rest of a patient' s lifetime. If a patient misses dosing or doesn' t take all the prescribed drugs for a period of time, their HIV can rebound and may mutate and become resistant to treatment.

UBP is developing a novel antibody in the treatment of HIV that inhibits the entry of the virus into T cells, preventing the virus' replication. What makes our antibody unique is that it competes with HIV to bind to the same site on T cells, blocking their entry into the cell and preventing the virus' activity without generating resistant strains. Therefore, even drug-resistant HIV strains could be treated with this host-targeting antibody. After pre-clinical studies showing that our antibody arrested the viral spread of HIV, we continued with studies in human subjects in Phase 1, 2a and Phase 2 clinical trials with our antibody, UB-421. In our Phase 2 study, over 2-4 months, we saw that UB-421 as a single agent was highly effective at suppressing HIV levels and maintaining viral control in patients. We also saw indicators that UB-421 could reduce HIV proviral

DNA as well as bolster the patient’ s own immune system. This property suggests that UB-421 could also be a good candidate in developing a functional cure for HIV, a state of sustained ART-free HIV remission.

## 4. 臨床試驗的結果為何?

## What were the results of the clinical trial?

UB-421 的 II 期臨床試驗的結果榮獲發表在 2019 年 4 月 18 日出版的「新英格蘭醫學期刊」，本次試驗數據證明 UB-421 安全性與耐受性皆很良好。 使用 UB-421 單一藥方治療 HIV-1 感染者顯示出非常高的抑制病毒活性。與其他 ART 藥物相比，UB-421 可以降低 HIV 病毒載量和維持 HIV 病毒載量不反彈至少 16 週是前所未有的臨床數據。

The clinical results from our Phase 2 trial, which are presented in an article published in the April 18, 2019 issue of the New England Journal of Medicine, demonstrated UB-421 was a potent entry inhibitor. Using UB-421 as a single agent for the treatment of HIV-1 infected persons exhibited remarkably high viral suppression activity in all study participants that is unprecedented as compared to other ART by reducing the viral load and sustaining viral remission for at least 16 weeks.

## 5. 以 UB-421 治療可使 HIV 感染者獲得永久的症狀改善嗎？

## Will the treatment put an HIV patient in permanent remission?

目前，UB-421 已完成的臨床試驗僅為 16 週治療。 然而，我們已經觀察到非常令人鼓舞的數據：病患體內的原病毒 DNA (proviral DNA)因施打 UB-421 而減少。proviral DNA 是衡量潛伏性感染的 HIV 病毒儲庫 (HIV reservoirs)含量多寡的指標之一。 我們推測，長時間使用 UB-421 治療應可顯著減少 HIV 病毒儲庫含量到一個使病患即使在停止藥物治療後體內病毒載量也不會反彈的程度。 目前的 ART 療法只能作用在複製中的 HIV，且無法治癒 HIV 感染，而其原因是病患體內潛伏性的 HIV 病毒儲庫(HIV reservoirs)無法有效被身體免疫系統辨識。我們的實驗數據顯示，UB-421 可以減少或消除被 HIV 感染的 T 細胞中的潛伏性病毒儲庫 (latent reservoirs of HIV infected T cells)，同時防止病毒進一步傳播到未受感染的 T 細胞。 結合其他 HIV 研究結果，我們推測，UB-421 在與其他藥物適當的合併使用時，可以在 HIV 感染者身上實現功能性治癒 (functional cure)，亦即病患即使不服用或施打藥物也可長時間不出現 HIV 感染的症狀。

Currently, the completed clinical trials with UB-421 as a single agent are only up to 16 weeks of treatment. Yet, our preliminary data suggested a reduction of HIV proviral DNA, a marker for measuring the size of latently

infected HIV reservoirs. Although this needs to be confirmed in a larger trial, we believe this is an encouraging outcome that could potentially facilitate clearance of HIV reservoirs.

Current ART acts only on the life cycle of viruses and is non-curative due to the lifelong persistence of latent viral reservoirs which remain invisible to the immune system. We have seen signs that UB-421 as a single agent can reduce the latent reservoirs of HIV infected T cells while preventing further viral transmission to uninfected cells. Taken together with other HIV studies, we speculate that UB-421, when used in proper combination with ART, could lead to a "functional cure" in treated patients, who would have viral remission without a need of medication for a certain long period of time.

## 6. UB-421 治療與幹細胞移植療法比較，差異何在？

## How does this compare to stem cell transplants?

幹細胞移植是嚴重癌症患者的一種醫療程序，不適用於一般 HIV 感染患者，產生併發症機率與醫療風險極高。此外，並非所有接受幹細胞移植的 HIV 感染患者都能被治癒； 幹細胞移植療法的結果差異也很大，並且不可預測。 迄今為止，全世界經由幹細胞移植實現 HIV 感染症狀緩解的成功病例寥寥可數。 相較於幹細胞移植手術，施打 UB-421 抗體的治療方式是一種更安全、更適合一般 HIV 感染患者、醫療風險也明顯較低的治療方式。

Stem cell transplant is a medical procedure for seriously ill cancer patients, not for general HIV infected populations and it comes with a high probability of complications and risks. In addition, not all HIV patients who underwent stem cell transplants were cured; the outcome is highly variable and unpredictable. To date, there are only a few cases in the world that show the success of achieving HIV remission by stem cell transplant. Compared to a stem cell transplant procedure, our UB-421 antibody treatment is more suitable for patient populations and the risks may be significantly lower.

## 7. UB-421 的使用是否有針對特定族群？

## Is there a specific patient population you are targeting?

UB-421 的獨特性質顯示其可適用所有 HIV 感染患者。我們正在規劃其他針對不同 HIV 感染者族群的臨床試驗，包括 HIV 含量已被穩定壓抑的患者，以及不再對 ART 療法有反應(對 ART 藥物失效)的患者。

UB-421’ s unique properties mean that it is applicable for almost all HIV patient populations. UB-421’ s binding affinity to its target site has been shown to be the same in four studied ethnic populations. We are planning additional trials on UB-421 for a variety of patient populations including those with stably suppressed HIV and patients who are no longer responding to ART.

## 8. 使用單株抗體藥品可能會面臨哪些挑戰？

## What are some of the challenges associated with using a monoclonal antibody product?

與有機小分子藥物不同，抗體療法因注射藥物中含有大量免疫球蛋白(Immunoglobulin)，必須經由靜脈輸注 (infusion)、肌肉或皮下注射(injection) 給予 病患。靜脈或肌肉注射的程序需要在診所或醫院環境中由醫務人員執行;而皮下注射程序可在醫院或患者居家中進行。輸注 (infusion)或注射 (injection) 有可能出現輸注反應 (infusion reaction)和注射部位反應。 抗體藥物具有顯著的優點：(1)抗體具有較長半衰期，並且可以較低頻率給藥 (例如每週，半月或甚至每月給藥)，(2)蛋白質藥物對於肝臟，腎臟等具有較低的毒性，以及 (3)某些抗體藥物，例如 UB-421，可以產生有益的免疫調節作用，這是小分子藥物無法實現的。

Unlike organic small molecule drugs, antibody therapies contain large immunoglobulin proteins that have to be administered by injection, either via infusion, intramuscular or subcutaneous injections. For infusion or intramuscular injection the procedure requires medical personnel at a clinic or hospital setting; while the subcutaneous injection procedure can

be performed by patients at home. There are common adverse effects associated with infusion or injection, such as infusion reactions and injection site reactions.

Nevertheless, there are significant benefits with antibody drugs: 1) antibodies have long half-lives and can be administered with less frequent dosing schedule (such as administering weekly, semi-monthly or even monthly), 2) biological protein drugs have lower toxicities to liver, kidneys, etc., and 3) certain antibody drugs, such as UB-421, can exhibit beneficial immunomodulatory effects that cannot be achieved by small molecule drugs.

## 9. UB-421 的臨床試驗在哪裡進行？ 會在美國進行臨床試驗嗎？

## Where did the trial take place? Can we expect trials in the United States?

已完成的第 1 期，2a 期和 2 期臨床試驗是在台灣進行。UBP 正在拓展 UB-421 臨床至其他國家。我們將在台灣、中國和泰國進行以 UB-421 單一藥物替代 ART 療法的 3 期多區域、多中心試驗。 針對多重抗藥性 HIV 感染人群的試驗將在美國和中國進行。與 NIH / NIAID 合作的功能性治癒第二期臨床試驗正在台灣進行中。同時，我司亦正籌備第二個功能性治癒二期臨床試驗，預備在中國或台灣進行。

The completed Phase 1, 2a and 2 trials were conducted in Taiwan. UBP is expanding the trials with UB-421 to other countries. The phase 3 multi-regional multi-center trial with UB-421 monotherapy as substitution for ART will be conducted in Taiwan, China and Thailand. The trial for multi-drug resistance population will be conducted in the US and China. The phase 2 functional cure trial in collaboration with NIH/NIAID is being conducted in Taiwan. At the same time, we are preparing the second phase 2 functional cure trial that will be conducted in China or Taiwan.

## 10. UBP 接下來有哪些計畫？

## What next steps can we expect from UBP?

接下來將有許多全球性的、不同階段的臨床試驗被規劃進行。已經獲得監管機構核准的試驗將在未來幾個月內啟動。

此外，UBP 正在紐約長島建立辦公室，也正在中國子公司建立臨床和法規發展中心(位於上海)，以及 GMP 生產工廠(位於揚州)。這些營運據點的團隊正在準備於美國和中國推展幾項臨床試驗。

近期，我們正在計劃：

(a) UB-421 單一藥物用於替代治療已經穩定使用 ART 療法並已穩定控制 HIV 病毒(aviremic: VL

(b) 開放標籤、多中心、應用於功能性治癒 HIV 感染 2 期 臨床試驗。該試驗 IND 已在台灣獲 TFDA 核准並執行中，試驗內容主要為探討 UB-421 對於減少 HIV 前病毒 DNA(pro-viral DNA)的有效性，而 pro-viral DNA 是評量受感染的潛伏性的 HIV 儲存庫(latently infected HIV reservoirs)大小的重要指標之一。我們的長期合作夥伴 NIH / NIAID 亦將參與這項研究，他們將使用高靈敏度的 PCR 來檢測 UB-421 治療期間 HIV 儲存庫的減少程度。類似內容的 2 期臨床 IND 也已獲得中國主管機關核准。

(c)　一項 3 期、開放標籤、多國多中心、以 UB-421 作為最佳背景治療(optimal background therapy)的附加藥物、用於治療多重抗藥性 HIV 感染的試驗。該試驗 IND 獲得中國與台灣 FDA 核准執行，目前正在準備進行泰國 FDA 的 IND 申請。

There are a number of clinical trials being planned globally in various stages. Those with regulatory approvals will be initiated in the coming months.

In addition, UBP is establishing liaison offices in Long island, NY, and subsidiary companies in China, including a clinical and regulatory development center in Shanghai, and a GMP manufacturing plant in Yangzhou. These are in preparation for the launch of several clinical trials in the US and China.

Near term, we are planning:

a) A Phase 3 trial for UB-421 as a substitution for ART in the treatment of experienced aviremic (viral load

b) A Phase 2 open label, multi-center, trial for functional cure indication. It is conducting in Taiwan to study the effectiveness of UB-421 in the reduction of HIV proviral DNA, a marker for measuring the size of latently

infected HIV reservoirs. Our longtime collaborator at NIH/NIAID will participate in this study, applying their highly sensitive PCR assays in determining the reduction of HIV reservoirs during UB-421 treatment.

c) A Phase 3, open label, MRCT trial for the treatment of multi-drug resistance with UB-421 as an add-on agent to the optimal background therapy. The trial has obtained Taiwan and China FDA approval and is currently preparing to have IND submission to Thai regulatory.

## 11. 美國國家衛生研究院/美國國家過敏與傳染病研究所與聯生藥之間的合作關係為何?

## What is the nature of collaboration with NIH / NIAID (National Institute of Allergy and Infectious Diseases)?

a) 聯生藥自 2015 年起即開始與美國國家過敏與傳染病研究所所長 Dr. Anthony Fauci 實驗室的免疫病毒科主任，Dr. Tae-Wook Chun，開始 UB-421 的合作。Dr. Chun 及其團隊為 2019 年 4 月 18 日發表於 NEJM 論文的共同作者。

b) Dr. Chun 及其團隊進行了一系列重要實驗證實 UB-421 的效力，包括:

1) UB-421 可以與 T 細胞上的 CD4 受體結合，藉此阻斷 HIV 病毒進入宿主細胞。Dr. Chun 證明 UB-421 對美國地區的四大主要人種 (高加索人、非洲裔美國人、西班牙人、亞洲人) 具有相同的效力。此實驗數據亦包含在 2019 年 4 月 18 日發表於 NEJM 的論文中。

2) 在擬人化小鼠模型中單次注射 UB-421 可以抑制 HIV 病毒生長達 49 天。

3) UB-421 能有效中和(neutralize)已對至少 4 種不同的抗 HIV 抗體，即「廣泛中和抗體 (broadly neutralizing antibodies)」，產生抗藥性的 HIV 病

毒。其中之一為 NIHID 自行開發的 VRC01 抗體，此實驗數據已發表在 2016 年 11 月 9 日 Dr. Chun 發表於 NEJM 的論文中。

4) UB-421 可以重新激活 HIV 感染病患中潛伏於 T 細胞內的 HIV 病毒，而把潛伏的 HIV 病毒再度活化為根絕潛伏性 HIV 病毒庫(latent HIV reservoirs)的第一步。

c) 聯生藥已與 NIAID 簽署合作合約，Dr. Chun 將參與我們即將展開的功能性治癒 HIV 臨床試驗。Dr. Chun 和其團隊將以最精密的科技，digital PCR，來測量病人在使用 UB-421 的期間，潛伏 HIV 病毒減少的量。該臨床團隊亦有興趣參與我們多重抗藥性的臨床試驗。

a) United Biopharma has been collaborating with Dr. Tae-Wook Chun, Chief of Immunovirology Unit and his lab at NIAID since 2015. Dr. Chun and his associates are the co-authors of the UBP’ s article on 2019-Apr-18 issue of NEJM.

b) Dr. Chun and his staffs performed a number of important experiments to prove UB-421’ s effectiveness, such as:

1) UB-421 binds to CD4 receptors on immune T cells, the first step of blocking HIV entry, with same effectiveness in four major ethnic

populations in the United States, including Caucasian, African American, Hispanic and Asian. This data is included on 2019-Apr-18 issue of NEJM.

2) A single injection of UB-421 can suppress HIV growth up to 49 days in humanized mouse model.

3) UB-421 is effective in neutralizing the HIV viruses resistant to at least 4 different kinds of anti-HIV antibodies, the so called "broadly neutralizing antibodies", currently being studied in clinical trials. One of them is VRC01, being developed by NIAID itself. This data was published in Dr. Chun's article in the November 9, 2016 issue of NEJM.

4) UB-421 is able to reactivate latently infected HIV virus from immune T cells of HIV patients. This is the critical first step to eradicate the latent HIV reservoirs.

c) United Biopharma has signed agreement with NIAID for Dr. Chun to participate in our upcoming clinical trials for functional cure indication. He and his staffs will use the most sensitive PCR assays to measure the reduction of HIV proviral DNA in patients during the treatment with UB-421.

## 12. UB-421 的潛在適應症有哪些？

## What are potential indications for UB-421?

對於治療 HIV 感染，UB-421 可能有四種適應症：

a)替代 ART：UB-421 單藥於穩定使用 ART 且體內 HIV 載量被穩定抑制的患者上用於替代 ART 療法。

b)多重抗藥性：以 UB-421 聯合 ART 藥物的最佳背景方案(optimal background regimen)用於治療已對多種 ART 藥物產生抗藥性的 ART 治療失敗患者。

c) 一線藥物治療失敗：以 UB-421 聯合 ART 藥物用於治療對一線抗 HIV 藥物治療失敗的患者。

d) 功能性治癒：以 UB-421 聯合 ART 藥物用於治療所有被 HIV 感染並具有顯著巨大的潛伏性 HIV 儲庫 (latent HIV reservoirs)的患者。

UB-421 is developed for treatment of HIV infection potentially in four different indications:

a) Substitution – UB-421 monotherapy (single agent treatment) for substitution of ART in ART experienced patients whose viral load is stably suppressed.

b) Multi-drug resistance - combination therapy with UB-421 together with optimal background regimen of ART drugs for patients who fail treatment and show resistance to multiple classes of ART drugs.

c) First line failure – combination therapy of UB-421 and ART for patients who fail treatment from taking the first line ART.

d) Functional cure – combination therapy with UB-421 together with ART for all patients infected with HIV and have a significant size of latent HIV reservoirs.

## 13. UB-421 與臨床試驗中的廣泛中和抗體有何不同？

## How is UB-421 different from broadly neutralizing antibodies already in clinical trials?

病毒導向的廣泛中和抗體(broadly neutralizing antibodies，bNAbs)乃是標靶在 HIV 表面蛋白 gp120，因此很容易因為 HIV 突變就產生抗 bNAbs 病毒株，而宿主導向的 UB-421 能完全抑制所有 HIV 變體的感染。UB-421 單一用藥治療未發生病毒反彈(viral rebound)，而以 bNAbs 作為單一藥物治療，病毒抗藥性則迅速產生。對 bNAbs 具有抗性的突變體(例如 VRC01,3BNC117,10-1074 和 PGT121)可被 UB-421 高靈敏的抑制。

The pipeline of United Biopharma consists of therapeutic antibody drugs in three major disease areas, infectious disease, immune disorder and oncology. In addition to UB-421, there are 5 products in various stages of development.

The virus-directing broadly neutralizing antibodies (bNAbs) target HIV-gp120 where resistance mutation can easily develop, while the host-directing UB-421 is capable of complete inhibition of infection by all variants of HIV.

No viral rebound occurred with UB-421 monotherapy, while viral resistance rapidly developed to bNAbs as a single agent. Moreover, participants enrolled to the bNAb' s trial need to be pre-screened to exclude those already showing resistance to the study drugs. HIV mutants resistant to bNAbs (e.g., VRC01, 3BNC117, 10-1074, and PGT121) are highly sensitive to the inhibition by UB-421. This data was published in the November 9, 2016 issue of NEJM.

## 14. UB-421 抗體如何生產?由誰製造?

## How is the UB-421 antibody made and who manufactures the product?

我們在台灣聯合生物製藥公司的 GMP 工廠生產 UB-421，我們的生產能力已擴展到 UBP 在中國子公司的揚州廠。 UB-421 製造工藝已提升至商業規模，採用 2,000L、一次性生物反應器和最先進的下游層析純化系統。 我們的自有細胞株可生產 8 ~ 10 克/升的 UB-421，此工藝水平在抗體生產領域是屬於高紀錄。

We manufacture UB-421 at United Biopharma’ s GMP facilities in Taiwan, and the production capacity has expanded to UBP Greater China’ s facility in Yangzhou, China. The manufacturing process has been upgraded to commercial scale, employing 2000L single-use bioreactor and state-of-the-art downstream chromatography system.

We are developing a proprietary cell line and cell culturing which can produce UB-421 at 8 to 10 grams per liter., again a record of high yield from production level aspect.