Xora Venture Pioneers

in collaboration with SMART/MIT

Eligible Programs:
SFMBA, EMBA, PhD

The Xora Venture Pioneers in Life Science Entrepreneurship at SMART/MIT offers entrepreneurs the opportunity to create new ventures based on compelling life science technologies spinning out of the Singapore research ecosystem.

Over the past three decades, Singapore has invested heavily in building world-class basic research and clinical infrastructure and talent. More recently, a significant and collective effort, from both public and private interests, is being directed to translational activities and research commercialization efforts.

Xora Innovation, an early-stage investment platform of Temasek Holdings, is one such cornerstone endeavor dedicated to building global, deep science ventures alongside ambitious founders.

Xora Innovation has partnered with SMART, the Singapore-MIT Alliance for Research and Technology, to launch the Xora Venture Pioneers in Life Science Entrepreneurship. Founded in 2007 by MIT and the National Research Foundation of Singapore (NRF), SMART is MIT's first and, to-date, only research center outside of the United States. It is MIT's largest international collaborative research program, with research performed in SMART labs by faculty, graduate students and post-docs with MIT appointments and affiliations. The SMART Innovation Centre, modeled after the Deshpande Center for Technological Innovation at MIT, drives technology transfer at SMART, especially via entrepreneurial paths, leveraging MIT's heritage in spinning off successful deep tech enterprises.

The Venture Pioneers program provides strategic and practical resources and an exceptionally unique opportunity for venture pioneers ***to create, to lead, and to build***, with the support of world-class investors that possess an unrelenting commitment to making a difference and delivering impact for humanity across the globe.

As a Xora Venture Pioneer, you will have received an advanced technical and/or business degree from a top tier university in the past 7 years *and* possess actual entrepreneurial experience or a compelling demonstration of entrepreneurial intent and spark. Ideally, you will have struggled or failed at something big in your life and bounced back, armed with lessons learned, a healthy dose of humility, and a heightened awareness of what it takes to lead and press forward with conviction.

Pioneers are supported through active mentoring by a global network of advisors with deep and specific operating experience in building and scaling Life Sciences ventures. An immersive orientation and ongoing training and networking elements enable Fellows to quickly and effectively situate, chart strategies and plans, and position for successful fundraising and team building. New ventures founded by Xora Fellows will be fast-tracked for pre-seed investment by Xora Innovation, to support formation, technology transfer, business planning and other launch activities.

The 12-month program, which starts on or about July 1, is a full-time opportunity based in Singapore. Xora Venture Pioneers will receive basic healthcare and housing benefits and a living stipend of $110,000 for the term of the program. If a Pioneer transitions to a leadership role in a new venture, it's expected that s/he will negotiate a market-rate compensation package at that time.

PROJECTS:

- **BIOENGINEERED PHAGE PLATFORM**
- **DEIMMUNIZING AAV WITH A COUPLED MACHINE LEARNING AND EXPERIMENTAL PLATFORM**
- **IMPROVED T-CELLS FOR SOLID TUMOR TREATMENT**
- **NOVEL GENE/CELL THERAPY PLATFORM**
- **PLATFORM FOR DEVELOPING SELECTIVE AND PATENT NEUROKININ RECEPTOR AGONISTS**
- **PRECISION BIOMANUFACTURING OF ANTIBODY-DRUG CONJUGATES**

BIOENGINEERED PHAGE PLATFORM

Antimicrobial resistance is a global threat. The World Health Organization has produced a list of priority pathogens comprising "12 families of bacteria that pose the greatest threat to human health"; there is an urgent need for solutions addressing this crisis, not only with new antibiotics, but also with alternative treatments. Bacteriophage (phage) have regained active interest by both the scientific and clinical community. In 2019, for the first time since their discovery over a century ago, scientists have engineered a mycobacteriophage targeting a highly drug resistant *Mycobacterium abscessus* and successfully treated an infected cystic fibrosis patient.

Phage provide a platform for rapidly genetically engineering these agents to attack drug resistant bacteria. A Team at NUS has developed a battery of *recombinant phages* for the treatment of infections in skin and soft tissue infections (SSTIs) and modulate gastrointestinal tract (GI) infections that is novel, specific and applicable. Selected phages are genetically re-engineered to generate patentable therapy and also reduce the risk of microbial resistance.

The team is taking a two tier, diagnostic and therapeutic approach to drive commercial and clinical impact from its phage engineering platform:

1) Rapid diagnosis of hospital acquired infections

New research estimates that the 2019 cost of sepsis care for in-patient and skilled nursing facility (SNF) admissions was more than US$62 billion. The 6-month mortality rate among fee-for-service Medicare beneficiaries in the US with an inpatient admission was about 60% for septic shock, which is the most severe form of sepsis. These data come from the largest sepsis study ever conducted with Medicare data. Sepsis is diagnosed in at least 1.7 million adults annually in the US according to the CDC and about 270,000 Americans die from sepsis each year – 1 in 3 patients who die in hospitals are diagnosed with sepsis.

The team is developing a simple, rapid point-of-care test (POCT) with phage designed through their platform that can be delivered in a self-contained cartridge used with a hand-held device.

2) Therapeutics

Nosocomial infections are a major healthcare problem throughout the world, affecting both developed countries as well as resource-limited countries. The WHO reports that hospital-acquired infections are among the major causes of death and increased morbidity among hospitalized patients and estimates that more than 1.4 million people. It is estimated that 50% of hospital-acquired (nosocomial) infections are resistant to first-line anti-infective therapies. The market opportunity for antibiotics is large, with the market estimated at $44.7 billion in annual sales globally in 2020.

With the growing threat of antimicrobial resistance, this bioengineered phage platform can be further developed to provide safe, efficacious and cost effective therapeutics as an alternative to traditional antibiotics.

The Phage Engineering Platform will be used to develop phages for rapid diagnostics and targeted therapeutic products for nosocomial and drug-resistant bacterial infections. The Team is looking for a CXO who will share their vision and help form and drive the new venture to commercial and clinical impact.

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DEIMMUNIZING AAV WITH A COUPLED MACHINE LEARNING AND EXPERIMENTAL PLATFORM

Immune response is a major problem limiting the safety and efficacy of gene therapy and protein therapeutics. Currently patient specific immune responses against AAV gene therapy vectors limit efficacy in two ways: 1) many patients have pre-existing anti-AAV antibody and T-cell responses and are currently ineligible for therapy; and 2) gene therapies can only be dosed once because patients develop inactivating immune responses against subsequent dosages. An MIT team has developed an innovative platform integrating machine learning and high throughput experimental methods to design unique peptide variants to reduce the immunogenicity of Adeno Associated Virus (AAV) vectors used commercially in gene therapy.

The teams approach is initially focused on AAV2, widely used as a vector for gene therapies to target hemophilia A and B, retinal dystrophy, Alzheimer's disease, Parkinson's disease, epilepsy, and spinal muscular atrophy type 1 to name a few. However, the platform can be widely applied to de-immunogenize AAV serotypes and more broadly protein therapeutics. The team intends to apply their novel platform in the $200 billion gene therapy/proteins therapeutics market; they are looking for a CXO to scope out the best business strategy and help drive formation of a company that will help disrupt gene and peptide therapy.

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IMPROVED T-CELLS FOR SOLID TUMOR TREATMENT

Chimeric Antigen Receptors (CARs) repurpose T-cells to recognize a chosen tumor antigen, dramatically improving responses against cancers. While CAR treatments have revolutionized the treatment of B-cell cancers, the approach has found limited success for solid tumors, and even when effective can cause severe and even fatal side effects. Despite many proposed advances in engineered T-cell therapies, all described CAR designs have relied upon combining only a small number of signaling domains.

A team at MIT has created safer, more effective CARs via comprehensive searches identifying signaling component combinations that produce desirable phenotypes. Since there are over a million possible antigen receptor signaling combinations, creation and validation of individual engineered antigen receptor molecules is not a viable strategy. The team has developed a new approach to generate and assess more effective engineered T-cells, analogous to improving an antibody, by creating libraries and *'affinity maturing'* it for tighter binding; in this way, they create CAR signaling libraries to *'activity mature'* molecules to improve their anti-tumor responses. They then select from these libraries to find variants with greater target sensitivity, more robust proliferation, and/or altered effector functions.

The MIT team is applying its approach to create improved therapies for glioblastoma, a highly aggressive cancer with few effective treatments. They are selecting for CARs that persist better, kill more efficiently, and thrive in inhospitable tumor environments. The team believes there are broad therapeutic and commercial possibilities emanating from this discovery platform.

The Team is looking for a CXO who shares their vision and can lead the team to venture building and commercial impact.

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NOVEL GENE/CELL THERAPY PLATFORM

The development of CRISPR technology is transforming the genetic engineering of human cells for therapeutic applications. However, CRISPR has limitations including the limited size of its gene delivery payload and questionable safety due to possible random insertion into multiple locations in the human genome. A team at NTU has developed a novel gene editing tool, called Lambdagen, that overcomes the limitations of CRISPR for large genes that can be precisely inserted and thus opens a broad array of important cell therapy applications.

This patented platform, originally derived from bacteriophage lambda, is the first to: 1) deliver a large gene payload (up to 20,000 base pairs), 2) provide a seamless vector devoid of unwanted bacteria sequences, and 3) able to insert into one specific endogenous sequence in the human genome thereby increasing safety. The Lambdagen platform has been validated and shown safe with respect to genome stability and oncogene activity.

The advantages of the Lambdagen platform enables many cell therapy applications not possible with CRISPR. In diseases where a gene is defective at multiple locations, thus, requiring the entire gene to be replaced, the Lambdagen platform can uniquely achieve full gene insertion. The NTU team is initially developing hemophilia A and Wilson's disease cell therapy applications that require replacement of the entire wildtype gene. Both are orphan diseases that represent a large commercial opportunity. Second, the Lambdagen platform can insert a much larger gene payload for CAR-T or CAR-NK cancer immunotherapy. This opens up the possibility of targeting multiple CAR constructs as well as including novel control or deimmunizing features into the CAR-T or CAR-NK cells. The Team is working to make manufacturable allogenic CAR-NK cells for cancer immunotherapy.

The Team is looking for a CXO who can provide strategic direction, engage the pharma industry in collaboration and co-development partnerships, drive the new venture to attract investment funding and execute on product development in the global market.

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PLATFORM FOR DEVELOPING SELECTIVE AND PATENT NEUROKININ RECEPTOR AGONISTS

Neurokinin Receptors (NKRs) have been identified as important drug targets for several diseases. Unfortunately, due to low specificity and selectivity, endogenous neurokinins have caused severe adverse side effects. Thus, there is an unmet need for highly selective and potent ligands for each of the NKRs that can be used as systemically administered drugs to specifically target an NKR.

A team at NUS has evaluated the structure-function relationships of Siaiokinin, a neurokinin ortholog found in the saliva of *Aedes aegypti* mosquito. Using the functional analysis of more than 100 selectively deleted/substituted synthetic mutant siaiokinins, the team has identified very selective and potent agonists of NKIR, NK2R and NK3R. These NKR agonists have been tested in ex vivo and in vivo animal studies to demonstrate their potential as therapeutic agents:

a) NK1R agonists
   Anti-inflammatory agents for treating inflammatory diseases including chronic obstructive pulmonary disease (COPD), multiple sclerosis (MS), arthritis inflammation and systemic lupus enythematosus (SLE). As well as treatment of certain brain tumors that express NKIR, using targeted radiation therapy (TRT) by radio labelling the NK1R agonist.

b) NK3R agonists
   Augmentation of NK3R signaling plays an important role in ovulation and follicular maturation in females leading to ovulation. Current treatment using urinary gonadotropins is expensive and ineffective.

c) NK2R agonists
   Voiding dysfunctions of bladder is a common problem of elderly, the NK2R agonist can provide better control over bladder and bowel dysfunctions.

The team has developed the platform capability to target NKRs with highly potent and selective peptides. This platform has proven impact in designing next generation improved, selective agonists for a range of critical disease applications. The team is looking for a CXO with drug development expertise who can select the optimum opportunities to pursue and can drive the company to clinical and commercial impact.

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PRECISION BIOMANUFACTURING OF ANTIBODY-DRUG CONJUGATES

Antibody Drug Conjugates (ADC) are an important tool in addressing aggressive cancers; however, the current mode of synthesis generates heterogeneity in the final product that leads to variability in therapeutic efficacy. A team from MIT and NTU are creating a new venture based on an innovative platform technology called Enzyme-Mediated Antibody Conjugation (E-MAC) that address this problem. The patented platform provides precision in biomanufacturing of immunomodulatory Antibody Drug Conjugates (ADCs). E-MAC uses an enzyme, peptiligase (BUTE1) to recognise a conserved amino acid sequence and catalyses the efficient conjugation of peptides to proteins thus reducing the heterogeneity that impairs ADC performance.

Most of current ADC's are based on chemical conjugation of payloads onto the antibody that leads to heterogeneity of the final product; the payload is attached with little control at multiple sites causing variability in the drug-antibody (DAR) ratio. This heterogeneity, is detrimental to ADC efficacy and translates to frequent failure of ADCs in clinical trials. Moreover, chemical conjugation does not always ensure the safe release of the cytotoxic payload in the tumor or its vicinity. This leads to undesirable side effects that render the use of such molecules too dangerous for patient care. Other biotechnology companies have been formed with the promise of overcoming these hurdles. However, the technologies used are less efficient (NBE Therapeutics), more expensive (SutroBio, BrickBio) or too complex (Synaffix, Syndivia) to streamline the development of novel anticancer drugs. The capacity to rapidly design and synthesize highly homogeneous ADCs using a single conjugation step, with well-defined defined Drug-to-antibody-ratio, is unique to this platform.

In order to rapidly co-develop and bring to the market novel ADC's within the first 3 years of its existence, the venture hopes to partner with several innovative biotech companies at the forefront of target discovery in cancer therapies. These partnerships would bring in the know-how and expertise required to facilitate the expansion of the venture into a fully integrated bio-therapeutics company. The venture will also develop its own portfolio of targets through an active discovery program with a goal to bring three fully validated ADC's to the clinic within the next 5 years. This new venture is looking for a CXO and team that can drive their vision to commercial impact.

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