Eastern Canada Pandemic Preparedness Hub
Pôle de préparation aux pandémies de l'Est du Canada

PRIORITIES, VISION AND PROGRAM OF RESEARCH

EASTERN CANADA PANDEMIC PREPAREDNESS HUB

ANTICIPATING THE NEXT PANDEMICS AND OTHER EMERGING HEALTH THREATS IN CANADA

Canada was affected by many emerging infectious diseases and pandemics in the last two decades, including SARS in 2003, H1N1 in 2009 and the COVID-19 pandemic in 2020, which continues to impact all levels of society three years after onset. Ebola (2014) and Zika (2016), and human monkeypox (2022) were further warnings. The current COVID-19 pandemic revealed to all that the Canadian bio-innovation and manufacturing ecosystems were unprepared to meet such a challenge. This disruptive and tragic experience was a stark reminder of the devastating potential of pandemics on our vaunted health system, our economy, and society in general. Emerging infectious diseases are expected to increase with climate change as humans, animals and vectors of infection adapt their behavior and ecology. In many respects, the country was paralyzed: there were severe supply chain issues, shortfalls in manufacturing capacity and worse, the lack of highly qualified personnel (HQP) was glaring. Overall, academia-industry-government were not prepared to react in a coordinated fashion.

The proposed **Eastern Canada Pandemic Preparedness Hub (ECaPPH)** will become a key player in development of Canadian capacity to deal with the next pandemics. In close coordination with other funded CBRF Hubs, ECaPPH will build a national ecosystem that will become a major global contributor for detection of the next emerging threats and the development of appropriate national pandemic responses. This will be accomplished namely by the creation of a prepared workforce, and the implementation of coordinated responses including diagnostic and preventive measures and development of new therapies. These actions will be based on innovative Canadian science and biomanufacturing, including scaled processes and production. The Hub will take advantage of already existing academy-industry partnerships in the sector of AI-accelerated discovery and catalyze the creation of new ones.

ECaPPH will support the development of local supply of specialized reagents, therapeutics and vaccines in preparation for a pandemic, or when supply chains are weakened by geopolitical or climate hazards. ECaPPH will contribute to Canada's sustainable development strategy. The support of local production respectful of the environment (e.g. green chemistry) will also encourage a sustainable development strategy by reducing overseas production, as they are not always subject to strict environmental standards. A significant reduction in transport distances will also limit the ecological impact.

The ECaPPH will build an ecosystem of more than 50 participating organizations from all sectors (college, universities, industry, NGO, government) poised to cover the whole chain of innovation of life sciences to ensure pandemic preparedness, and ongoing inter-pandemic coordination. The ECaPPH will be partner with other CBRF-funded hubs to build a truly national network. Furthermore, ECaPPH partners strongly believe that pandemic science 'nationalism' is fundamentally ill-advised and not coherent with international reality. Thus, the broad international ties of many of the participating organizations in ECaPPH will also advocate for Canada to become a major worldwide contributor aiming to integrate pandemic preparedness and response with international initiatives at a planetary scale.

The ECaPPH's program will synergize the strengths of its partners. It will comprise: Surveillance, Biobanking, RNA-based approaches, Virology Research, Vaccines, Therapeutics, Cell therapies, AI, and Preclinical studies and models. These efforts will be embedded in a thriving and innovative Bioprocessing and manufacturing ecosystem and in our internationally recognized expertise to run clinical trials. ECaPPH will ensure that a network is in place for *C*ommercialization, *C*onstant dialogue with decisions makers, *C*ommunication with the public, and for Evaluation of our output.Through diverse, multi-sectorial partners, including some supported by the Government of Canada Strategic Innovation Fund (SIF), this proactive pandemic

preparedness chain will include the development of integrated HQP training programs for both the innovation segments of the chain, but also technical training to supply an expanding pool of personnel for a growing biomanufacturing base essential to quickly deliver diagnostics, vaccines and therapeutic solutions in the event of a pandemic.

ECAPPH PRIORITIES, VISION AND PROGRAM OF RESEARCH1

ECaPPH's vision is to transform the preparedness ecosystem in Canada by building a strong and interactive network of expert partners, by optimizing the current and upcoming infrastructures, and by nurturing training capacity. In this proposal, we describe how the entire ecosystem will be reinforced by addressing important gaps in the innovation chain identified during the COVID-19 pandemic. Our priority is to cultivate a collaborative ecosystem between all ECaPPH partners, but also with other CBRF Hubs and ongoing international efforts. In our first 4-5 years, the scientific priorities will focus on emerging diseases with a program of research that taps into the talents and capabilities of partners to be better prepared and to better respond to the next pandemics. Well-documented successes will ensure sustainability of ECaPPH by nurturing a thriving infrastructure and knowhow that will drive innovation in Canada. Our proposal is purposely broad-based and the result of a vetted process. Indeed, we are unsure of the etiological nature of the agent that will be responsible for the next pandemic and of the most effective countermeasures against it. Having diverse proven and established strategies in our preparedness toolbox will allow ECaPPH partners to be nimble to implement the most effective rapid response.

1. EARLY DETECTION AND GLOBAL SURVEILLANCE

A clear consensus emerging from our stakeholder's consultations for building ECaPPH pertained to the importance of being closely connected to surveillance systems. An effective integration of surveillance systems is essential to detect outbreaks quickly before they spread and become difficult to control. ECaPPH will therefore create a **surveillance working group** that will collaborate closely with other CBRF Hubs, and with provincial, federal, and international surveillance public health systems. The Group will swiftly communicate to ECaPPH partners information relevant to emerging threats that could initiate a rapid research response. Many actors and partners of ECaPPH have long-standing collaborations with provincial and national (PHAC) agencies, but also to international ones, such as the WHO Hub for Pandemic and Epidemic Intelligence (https://pandemichub.who.int). The ECaPPH surveillance working group will liaise with organisations in human and public health, but also with networks focused on emerging zoonotic infections, outbreaks, travel-related illnesses, environmental surveillance (e.g. wastewater testing during the COVID-19 pandemic), syndromic surveillance, and population immune surveillance. We need to be prepared for any emerging health threat. Hub partners include two veterinary schools, well aware that new threatening pathogens may have a zoonotic origin (https://grezosp.com) and ECaPPH's partners are involved in the creation of a newly budding international One Health network (https://prezode.org) developing and implementing methods to prevent zoonotic disease emergence. Climate change is affecting all life, and may accelerate emerging infections like anaplasmosis or Lyme disease. Although most recent pandemics have been of viral origins, antimicrobial resistance (AMR) is one of the most serious threat to global health. The surveillance working group will insure

[1] Please note that the scientific program and vision of ECaPPH is expressed without reference to any specific institution, industry, NFP, researchers or other organization. This vision is a collective effort to which all ECaPPH actors and partners are committed. In order to capture more specific reference to each of the ECaPPH's partners, please consult the "Capacity" section.

that AMR data derived from national and international public health surveillance programs will be communicated to ECaPPH partners.

Monitoring of emerging events is based on the existence of multiple (population, environmental, zoonotic, etc…) surveillance systems. ECaPPH will strive to provide tools to build an improved surveillance system by innovative research in diagnostics (see 2.2.1) but also in the integration of big data. With the unique current and next-generation AI-based capacity to process large datasets from surveillance systems, ECaPPH is well positioned to strengthen data sharing and secure information systems, in integrating health information with other contextual information, such as climate information social factors, and social media. This will allow standardisation of analytical tools and methods for better modeling to face future pandemics and for the detection of rare events likely to be missed by traditional surveillance methods in early stages of new pandemics.

2. NECESSITY TO BETTER IDENTIFY AND UNDERSTAND EMERGING DISEASES

2.1. BIOBANKING: EARLY ACCESS TO SAMPLES AND DATA

Access to relevant material, samples and databases is a prerequisite to respond adequately to microbial threats. The *Biobanque Québécoise de la COVID-19* (BQC19) has set a benchmark as a leading biobank in Canada and has achieved international recognition. There are numerous biobanks in Eastern Canada and ECaPPH will carry out a mapping exercise of biobanks deemed relevant, a resource that shall be most helpful to ECaPPH partners. ECaPPH will be in close contact with other CBRF Hubs to help remove barriers for an integrated virtual (not in a single site) national biobanking system, but also in developing guidelines for ethical and equitable access to bio-banked material. These efforts will facilitate collaborations involving academia and industry. Large cohorts of volunteers, infected patients and controls, as well as bio-banking of relevant target cell, including immune cells, biological specimens (ex: blood, stools, and other fluids and tissues) as well as isolated pathogens are of utmost importance. The cohort of enrolled volunteers should be diverse as per EDI considerations, including from hospitalized and community dwellings, from immunocompromised, treated, and members of vulnerable or traditionally underrepresented populations and adults and pediatric populations. The Hub will build on BQC19 and apply his AI expertise in creating portals for host and pathogen genomic sequence storage, curation and analysis (e.g. https://www.cgen.ca/project-overview, https://virusseq-dataportal.ca, sequences data portals). The resulting pathogen databases will permit the discovery and monitoring of potential new pathogens and variants of concern that may arise. We will seek to have a repository of isolated pathogens (and their key genes cloned into plasmids) that can be amplified and distributed for preclinical studies and to facilitate standardisation. Canada at present has limited access to the physical infrastructure and the efficient governance processes needed to manage this genomic information. ECaPPH will work with other CBRF Hubs and similar international organizations to identify strategies to optimize the use of biobanking data.

2.2 OVERVIEW OF THE DISCOVERY RESEARCH PROGRAM

ECaPPH, with the academic institutions and its partners, host outstanding scientists in Infection and Immunity research and practitioners who can provide rapid insights into emerging pathogens, including identification (Dx), preventive (e.g., vaccines) and therapeutic (e.g., antiviral, anti-inflammatory and supportive therapies) solutions. Some of the planned research topics include RNA-based approaches, biologics (such as antibodies) and cell therapies. These activities will be under the aegis of a strong bio-processing -manufacturing ecosystem receiving collaborative input and support from the AI community.

2.2.1 DIAGNOSTICS

The COVID-19 pandemic has underlined several informational challenges to determine who is infected and who is infectious at a given time. Technological limitations of both rapid diagnostics and continuous monitoring systems led to chains of

transmission disruption. Both our vaccine design and production as well as home testing for SARS-CoV-2 relied on other countries. Indeed, the Canadian BTNX rapid tests had to be manufactured abroad. In many respects, COVID-19 transformed the diagnostic landscape: for example, at-home testing and telemedicine have now become common practices. Eastern Canada has a vibrant ecosystem of academic researchers, startups and industry working towards next-generation diagnostics tests (whether molecular or immunoassays). Immunoassays (lateral flow, fluorescence based) have been central in mitigating the effects of the COVID-19 pandemic. However, single molecule immunoassays (SIMOA) set a new standard that we will emulate and strive to adapt to point-of-care (POC) diagnosis by new assay designs and protocols. The bioprocessing component of ECaPPH (Section 3.0) will be developed to rapidly provide proteins and antibodies as screening platforms to detect viral variants or monitor immune responses. PCR (DNA or reverse-transcribed RNA) remains the gold standard for molecular diagnostics, but the approach is time-consuming and depends on advanced equipment. New alternatives, including simplified PCR systems, such as isothermal amplification coupled to CRISPR technology, have the potential to bring molecular tests to POC and home testing. The ECaPPH ecosystem has proven expertise in integrating molecular diagnostics, microfluidics and nanotechnology that could greatly facilitate POC and home testing as well as contact tracing. ECaPPH partners are well positioned to **develop new diagnostic methods,** such as nanomaterials-based biosensing and nano/microfluidic lab-on-chips, which are inexpensive to build and easy to use. We have proven expertise in producing such tests. The translation of diagnostics to end-users is dependent on transitioning from artisanal research tests to manufacturing procedures amenable to mass production. We have tremendous strengths in microfabrication, additive manufacturing and in injection molding, which we will nurture and exploit for commercialization. As diagnostics become increasingly connected to digital health databases, they can be integrated into surveillance networks and AI-based analyses for tracking positivity rate, disease hot spots and evolution.

The ECaPPH program will also include development of new diagnostic tools based on cutting-edge imaging technologies, like smFISH, that uses visualization of RNA to study host-pathogen interactions at the level of the single cell providing insights into pathogenesis. The imaging technologies extend to X-Ray, Cryo-EM, Cryo-ET that allow high resolution CL2/3 pathogens images. ECaPPH members have state of the art genomics infrastructure. We contend that Next-generation Sequencing (NGS) is likely to play a central role in a paradigm shift in diagnostics. Sequencing of new pathogens is a crucial initial step in the development of PCR-based assays and candidate vaccines. NGS is also essential for the early identification of emerging variants, and can provide key information in the context of evolving AMR. NGS technology is continuously being miniaturized and simplified in terms of procedures and read outs. For example, the highly portable Oxford Nanopore Technology is now deployed in many clinical microbiology laboratories with significant impact on patient management. The field of diagnostics and NGS including metagenomics are closely integrated in our objective of contributing to a nimble quick surveillance system. These efforts will require strong bioinformatics skills; a capacity strongly represented in ECaPPH.

2.2.2 RNA-BASED APPROACHES

RNA-based approaches include investigations of viral and host protein-coding mRNAs as well as the large variety of non-coding host RNAs that reflect the genetic and environmental makeup of an individual. Importantly, RNA research has led to breakthroughs in the development of diagnostic tools and therapeutics as best exemplified by the mRNA vaccines against SARS-CoV-2. Drugs targeting RNA processes also holds great promise in our fights against pathogens and/or against host-based proteins altered during infections. The Hub is home to the largest multidisciplinary community of internationally recognized RNA scientists in Canada. These experts have the capacity to generate innovative knowledge in RNA research and to leverage their skills into applications. They have the capacity to develop RNA profiling and translatome approaches, RNA production and delivery systems, including vectors, strains, encapsulation methods, RNA stability for large-scale production, 3D-structure/function characterization of RNA and AI-based platform to identify potential drugs targeting viral RNAs.

The genetic make-up of an individual contributes to both susceptibility and response to emerging pathogens, including viral infections. The program will address host genetics, host immunity (e.g. antibody responses, cellular immunity). During the COVID-19 pandemic, ECaPPH researchers contributed to elucidation of markers of susceptibility/resistance to COVID-19 through genetic and functional genomics studies. This effort led to the identification of biomarkers and candidate targets for intervention and demonstrated that drugs targeting RNA splicing can be beneficial. These approaches exploit the latest NGS technologies (single molecule sequencing, single cell and spatial RNA sequencing, ATACseq) and deep immunophenotyping (flow cytometry, mass cytometry, high-content imaging). These cutting-edge tools for profiling RNAs can be used to gain insight into the viral life cycle to compare strains, to define immune response 'signatures' associated with recovery or progression to severe diseases and to both identify and evaluate anti-viral agents.

While NGS is a powerful approach to track viral evolution, it provides limited insight into viral gene expression patterns or how host cellular systems are usurped during active infection. Ribosome profiling is a powerful technique that uses NGS to track translation in living cells, providing insight into the quantity of proteins produced in cells, how this process is regulated at the individual mRNA level and potentially identifying novel drug targets. Ribosome profiling of viral infected cells (cytomegalovirus, Kaposi's sarcoma-associated herpesvirus, SARS-CoV-2) has unraveled unanticipated complexities in the coding capacity, identified novel small noncoding regulatory RNAs, and defined host cell translatome changes arising during infection. Application of ribosome profiling combined to quantitative proteomics methods to document viral infections is essential and enabling to understand virus-host interplay, correctly annotate virus protein expression, and identify pathways central for infection targeted by viruses – the latter being important to both discovery of antivirals and approaches to mitigate the impact of viral infection. We propose to create a facility to profile the translatomes of virus families of interest (e.g. coronaviruses, orthomyxoviruses including avian influenza, henipahviruses, Ebola viruses, etc), annotate the resulting information, and identify possible virus-specific vulnerabilities in the population.

ECaPPH support the development of candidate RNA therapies that build on RNA profiling and translatome approaches. Moreover, targeting RNA can simplify and speedup the drug discovery pipeline as it can rely on AI-based and rational approaches to identifying lead compounds. The critical mass of expert researchers in the academic sector can bring innovations up to a point where they are ready for uptake by the private sector. The Hub will build on the expertise to develop adapted LNP delivery systems and Canada's biomanufacturing to develop emerging RNA therapies for which the market is rapidly growing.

2.2.3 VACCINES

The hub will contribute to development and production of vaccines by biomanufacturing high potential human vaccine candidates for clinical evaluation that industry would not make upfront due to high risk or low potential economic benefits. In the context of the recent SARS-CoV-2 pandemic, lessons learned from the Coalition for Epidemic Preparedness Innovation (CEPI) must not be forgotten. The first vaccines available for SARS-CoV-2 resulted from CEPI-funding for basic discovery science and novel platform technologies, including the adenovirus-vectored vaccines and the highly successful mRNA vaccines. The remarkable diversity of SARS-CoV-2 vaccine candidates and the fact that many initially promising candidates failed due to limited efficacy or platform-specific adverse events not only support the underlying reason for the CBRF call for proposals but are also powerful reminders that Canada must not put all of its vaccine innovation 'eggs' in one basket and must control and maintain supply chain.

Both academic and industry experts in ECaPPH have deep expertise with tools needed to develop novel vaccines based on a wide range of platforms. These tools include a large number of well-defined *in vitro* (e.g. tissue culture, organoids), *ex vivo* (e.g. tissue explants, primary cells) and animal models, biocontainment facilities (see 2.2.7), well-characterized immune assays and state-of-the art clinical testing facilities from Phase 1 to global Phase 3/4 studies. ECaPPH also has unique tools at their

disposal including novel adjuvants (e.g. depot formulations, plant derived nanoparticles), new delivery tools (e.g. human cells, attenuated and non-replicating protozoal, bacterial and viral vectors, plant-made virus-like particles and other nanoparticles). The recent licensure of the first plant-made vaccine for human use (Cofivenz™ for SARS-CoV-2) by a key ECaPPH member is a good example of what collaboration between academic and industrial Hub members can accomplish. The NGS capabilities described in 2.2.1 and RNA work described in 2.2.2 will impact vaccine discovery both directly (e.g. candidate mRNA vaccines) and indirectly (e.g. variants, host-pathogen interactions, novel targets). Polysaccharide-based vaccines have a proven track record against bacterial pathogens but remain under-studied for viral pathogens despite their importance for host-viral interactions. The core of glycobiologists within ECaPPH will be instrumental in defining the potential of sugar based-vaccines for organisms of pandemic potential.

The development of novel vaccines capable to induce a broad protection against all variants of SARS-CoV-2, or influenza A viruses that caused more than 10 pandemics in the last 300 years, will be addressed by ECaPPH. Finally, Hub members are also world leaders in understanding and addressing vaccine hesitancy and resistance. Although the primary focus of the Hub will be developing vaccines to protect Canadians, ECaPPH members have a long-standing track-record and commitment to equity and global health. Because of the recent experience with limitations of SARS-CoV-2 vaccines (e.g. requirement for ultra-low temperature storage) and their mal-distribution, Hub members will include practical considerations in their vaccine development efforts in particular to reduce dependence on cold chains.

2.2.4 THERAPEUTICS

The ECaPPH strategy to discover new therapeutics is spearheaded by its leading screening AI capacity, as well as established commercial and proprietary chemical libraries that include antimicrobials and antivirals with known mechanisms of action. These libraries are geared towards structural and chemical property diversity and comprise over 185,000 compounds including both naturally-derived and synthetic compounds. The capacity to test these large collections of compounds will be provided by well- established screening centers that have a proven track-record of developing and scaling-up assays to identify biologically active molecules. Once hit compounds are identified, ECaPPH will take advantage of its internationally recognized expertise in medicinal chemistry to transform the hits into molecules to become a drug and progress to the clinic. To fill the need of small molecules (drug or chemical), the versatile continuous flow chemistry approach will also improve our capacity to respond quickly to demand. Many promising leads will likely be absent, even from the largest chemical libraries due to the extremely high number of possible chemical permutations. To overcome this limitation, we will leverage our world-class current and next-generation AI-driven prediction (Machine Learning (ML) and Deep Learning) to predict promising candidates, reaching well beyond the screened pool of compounds. A crucial component for any AI-guided drug discovery effort is robust input data – training datasets – to build accurate models using ML architectures. ECaPPH members have ample expertise in wet lab infection models required to build these training datasets. AI-guided and medicinal chemistry efforts will be complemented by drug repurposing studies that provide a more rapid path to clinic by reducing common regulatory hurdles. With a proven track record of accelerating translation of academic discoveries into clinical candidates, ECaPPH benefits from established supports in intellectual property protection, market assessment and business development and strategy. With this complementary research expertise, we will efficiently advance discoveries into and through the drug development process.

2.2.5 BIOLOGICS

The past 2 decades have seen a revolution in our approach to therapeutic immunosuppression. We have moved from relying on broadly active traditional medications (e.g. steroids) toward more specific agents that target single receptors, cytokines, specific viruses or cell types, using monoclonal antibodies, fusion proteins, or targeted small molecules. ECaPPH partners have identified mAbs able to neutralize SARS-CoV-2 (COVID-19) and all variants of concern that have emerged since the start of the

pandemic. Currently in Phase 1 and 2 clinical programs for treatment of symptomatic patients with SARS-CoV-2, the candidate drug is a combined product containing 3 recombinant human monoclonal antibodies that specifically bind to distinct regions of the COVID-19 spike protein. Another drug candidate was identified during the pandemic and successfully passed pre-clinical evaluation. The Hub will provide connections to advance these discoveries into products, an ecosystem that must be nurtured and strengthened.

ECaPPH proposes to provide resources to accelerate development of candidate biologics, especially in the academic sector since public institutions can bring innovations to a point where they are ready for uptake by the private sector. The Hub will also build on its expertise to develop formulations administered by inhalation, some already in phase 1/2 clinical trials, which can provide an efficient, rapid and non-invasive method of delivery to the lungs via the airways in case of new respiratory pathogens.

2.2.6 CELL THERAPIES

Current antiviral treatments fail to cure certain chronic viral infections due to reservoirs in infected cells harboring latent viruses that persist for years. Therapies providing long-term control or able to eradicate the viral reservoir are required. Pathogen-specific effector T cells play a crucial role in control of acute infections in immunocompetent individuals, making adoptive T cell therapy an attractive alternative to currently used anti-infectious therapies. Cell therapies (e.g. stem cells or adoptive T cells) have a promising track record in treatment of viral infections in the setting of immunosuppression. Although no advanced clinical data are available regarding COVID-19, several teams globally have produced COVID-19-specific T cell candidates. Pathogen-specific T cells can be manufactured from patient (autologous) or prepared in advance from healthy individuals (allogeneic) and banked for rapid use in patients. Both approaches can be lifesaving and have caused few serious side effects. Hub partners have specific expertise to rapidly generate virus-specific T cells targeting Epstein-Barr Virus (EBV), with an ongoing trial in transplant patients, and are extending their work for other viruses. This expertise will be leveraged for future threats through expansion of current infrastructure. Enhancement of these therapies by genome editing is highly desirable to increase specificity and function of engineered cells. Allogenic therapy based on mesenchymal stem/stromal cells has shown benefit in COVID-19 patients with inflammation-mediated lung injury. ECaPPH will enhance regional capacity in development of immunotherapies and tissue repair to address acute and chronic effects of pathogens, and support development of cell and gene therapies to alleviate chronic conditions following infection. The Hub aims to develop scalable processes for cell therapies, both as a direct therapy, for example as immunomodulators to lower or enhance the immune system response, but also indirectly to produce cells that could be used for basic questions. ECaPPH members are already interacting with other cell therapy hubs in Canada and across the world showcasing their expertise (clean room, participation in CAR-T, CAR-NK and other immunotherapy trials) in cell therapy manufacturing for clinical applications.

2.2.7. PRECLINICAL STUDIES AND MODELS

Preclinical models are essential prior to drug testing in humans. These are categorized as *in vitro* or *in vivo*, although *ex vivo* models are also emerging. The ECaPPH ecosystem has considerable expertise with such preclinical systems. Conventional cell lines are often the first choice when studying viral pathogens and are suitable for producing large amounts of pathogens for development of diagnostic tools or for large-scale drug screening platforms. Nonetheless, these models have limitations and do not represent the complexity and 3D architecture compared to natural infection sites and lack biological aspects such as human immune responses. Primary culture systems provide more physiological models but the new paradigm for in vitro model systems consists of 3D cell cultures and in particular human organoids, where cultured, organoids provide miniature versions of an organ as a platform for drug development. More advanced *in vitro* preclinical models consist of organ-on-a-chip and bioprinted models bridging microfluidics, vascular systems and multicellular 3D cultures enabling recapitulation of cellular interactions, closely mimicking organ function and creating a scalable platform to investigate both interactions with

pathogens and pharmacological effects of biomolecules. We have already engineered iPSC lines that can be used to generate numerous functional cells types important for drug discovery related to pandemic preparation as monolayers in organoid models while considering between-patient susceptibility to infection and immunological responses for personalized medicine.

ECaPPH members will constantly improve development in human cell and tissue models. Similarly, 3D organoids or organ-on-a-chip innovations can be co-designed by biologists and engineers to mimic various human organs and can reduce animal usage. These *in vitro* systems can sometimes even substitute for animal models when the latter are prohibitively expensive, difficult to work with or simply do not exist. Yet animal studies remain critical in pre-clinical development of novel countermeasures. ECaPPH has the capacity to perform animal studies with various levels 2 and 3 pathogen containment whether they are bacteria, fungi, parasites, or viruses. A pending application would eventually allow manipulation of level 4 pathogens at ECaPPH. Mice, hamsters, and ferrets are small animal workhorses for *in vivo* model of infections. ECaPPH have also the capacity to generate humanized mice that can be transplanted with human tissues, which are primary target of specific viruses. All these small animal models allow studies on transmission and pathogenesis of microorganisms as well as evaluation of drugs, vaccines and biologics. No single small animal model exists for all pathogens, and use of any given model depends on the pathogen and on the type of intervention being tested. Indeed, if mice are often the preferred small animal model (cost, abundant offspring, tools available to create transgenic animals or expressing specific receptors, controlled microbiota), other animals also have specific advantages. For example, ferrets are often used to study respiratory viruses because their respiratory tract anatomically resembles that of humans. One distinctive feature of ECaPPH is our capacity to use non-human primate (NHP) infectious models with CL2 pathogens. With two veterinary schools, ECaPPH will can conduct trials in other larger animal species (e.g. pigs), if necessary. Last, the controlled human infection model (CHIM), already possible at ECaPPH, is a rapidly growing strategy for preclinical studies as they have the potential to accelerate development of therapeutics and vaccines directly in humans.

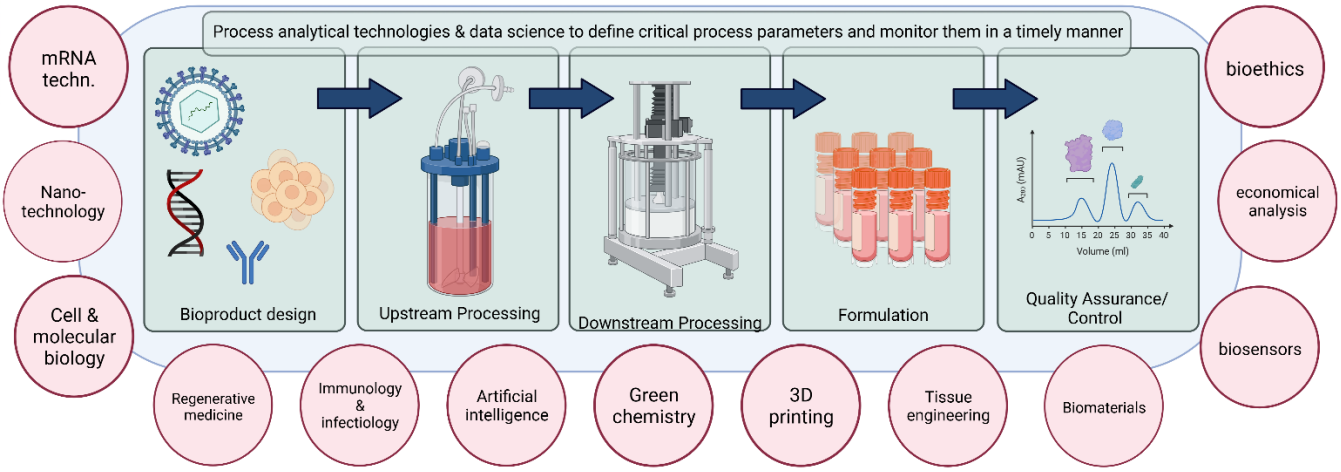
3. BIOPROCESSING AND MANUFACTURING

Sufficient biomanufacturing capacity is one Canada's main challenges as observed during the COVID-19 pandemic. Eastern Canada has a long-standing and close-knit bioprocess engineering community across academic units both at the university and college (CCTT-CEGEP) levels, with direct ties to the National Research Council Human Health Therapeutics Center. Infrastructure and expertise are available to produce a broad portfolio of biotherapeutics addressing critical roles in pandemic preparedness. These range from cell-free and microbial systems to production of small molecules including DNA or RNA, to animal cells and manufacture of complex biomolecules such as recombinant antibodies, viral vaccines, and even human cells for transplantation or high-throughput disease modeling. Despite the diversity of bioproducts, common engineering challenges emerge when scaling up bioprocesses under strict sterility and quality requirements imposed by current good manufacturing practice (cGMP). Our vision is to cement the existing continuum between colleges/CCTT, universities, the NRC and industry to create an integrated platform that would be unique worldwide. To achieve this, existing and enhanced training initiatives and research infrastructure will be streamlined to support the biomanufacturing ecosystem. In the Table below, we have identified several challenges associated with biomanufacturing in Eastern Canada and elsewhere. As a result, development of such a streamlined system within ECaPPH could be leveraged across the country, through other CBRF Hubs, and internationally.

Product category	Current strengths in Eastern Canada	Manufacturing challenges	Opportunities to build capacity
Small molecules and peptides, **antivirals, immunomodulators, or biomolecules to alleviate symptoms**	Production of bioactive molecules in engineered microorganisms. Biosynthesis of new-to-nature compounds for the development of new pharmaceuticals; Expertise in continuous flow synthesis allowing for a rapid synthesis of nearly any new therapeutic essays or to counter supply chain challenges that could affect Canadian industry	Long trial-and-error iterative cycles; Cost of production at-scale; Degradation of certain biomolecules	High-throughput screening for genome editing & construction of libraries of biological parts; Automate processes and sampling methods; Integrate machine learning to optimize biotherapeutic design and process control exploiting big data; Engineer bioreactors and culture systems tailored towards specialized applications Develop improved scale-down strategies that can easily be repurposed for different products; Implement continuous processing and process intensification to reduce cost; Optimize formulation and delivery systems to stabilize and deliver bioproducts; Coordination between cGMP platforms and cost reduction
DNA, RNA, and other nucleic acid-based technologies: Used as vaccines or templates	Collaborative environment including NRC, industry (e.g. Moderna) to build capacity. Pan-canadian RNA consortium being established	Thermal lability; Complex distribution logistics; Inefficient delivery in some cases	
Recombinant proteins: **Vaccines, agents that block viral interactions with receptors, immunomodulators. Proteins for Dx.**	Production of recombinant antibodies, viral-like particles, shuttle proteins to deliver cargo, peptides, receptor fragments, enzymes, self-assembling proteins & protein-based materials	Losses during purification Gram amounts required for certain applications: high cost; Difficulty to control product quality	
Viral vectors: **Used as vaccines and for cell & gene therapies**	Adenovirus, newcastle disease virus, VSV produced in HEK 293, Vero cell lines. iPSC expression platforms developed with NRC & academia. Cell culture platforms to respond to viral pandemics	Slow transition to continuous manufacturing; Low cost-effectiveness; formulation and delivery in particular mucosal delivery for rapid translation	
Human cells: **Immunotherapies, immunomodulators, tissue regeneration in chronic phases of infection. Used as models in personalized medicine.**	cGMP-level facilities for cell therapy processing. Immunotherapies and immunomodulatory cells, epithelial (skin & cornea) cells, pluripotent stem cells, organoid models, tissue engineering	Lot-to-lot, donor-to-donor variability; Logistics of scale-out; Complexity & variability of stem cell differentiation protocols; Need for automation/ standardization and access to cGMP suites at low cost	

One prominent biomanufacturing challenge is **process variability** impacting product safety, efficacy and clinical success. Population heterogeneity in cell cultures can lead to heterogeneity in final products. Sensitive cells such as animal primary cells and cell lines, primary human immune or stem cells can be highly impacted by their microenvironment, including mechanical factors such as shear stress or the plastics they contact. **Scaling up** (increasing volumes) or **scaling out** (increasing numbers of bioreactors) bioprocesses are non-trivial due to the impact of changes in cellular microenvironments. Another key challenge in biomanufacturing is reducing **cost**. During the research phase, products are often designed without considering the impact of early decisions on manufacturing challenges and outcomes. Even if high yields of products are obtained, purification steps can lead to significant losses. Once purified, ensuring stability of products can be problematic,

particularly when considering molecules that can be degraded, aggregate or for living cell products. For products such as mRNA, viral vaccines or gene and cell-based therapies, much of the active ingredient and hence the therapeutic action can be lost during delivery in contact with host tissues. Animal models can be inadequate to assess interactions of biotherapeutics with human tissues or the human immune system. These factors contribute to high R&D and manufacturing costs of biotherapeutics and bio-based diagnostic systems.



Aside from these key technical challenges, there are **critical gaps in the integration of biomanufacturing expertise and infrastructure** in Canada. The multitude of research networks, federal and provincial initiatives create fertile ground for biomanufacturing initiatives. However, there is no concerted action to link these initiatives – especially from engineering, scale-up and production perspectives. ECaPPH will facilitate integration of these efforts to support production of biomolecules and biologics in sufficient quantity and quality to perform various *in vitro* studies and preclinical and human trials. Our vision includes all aspects of the biomanufacturing process (see Fig. above). To address these key challenges, ECaPPH will encourage projects, ensuring that scale-up or scale-out potential and challenges are addressed throughout biomanufacturing steps, starting with bioproduct design. Systems for analysis and control of manufacturing processes based on timely measurements of critical quality parameters and performance attributes of raw and in-process materials will be developed. This will require new hardware & assays specific to monitor bioprocesses online, at-line and offline including macro/micro-fluidic systems and implementation of soft-sensors. An interface will be created between bioprocessing and AI expertise to optimally implement process monitoring, and optimization strategies. Digital twins and digital transformation of bioprocesses can reduce costs. There is also significant value in designing scale-down systems which better predict performance at scale. Rapid prototyping facilities including advanced polymer processing, 3D printing and computer-assisted design can produce tailored equipment and consumables for biomanufacturing or for use in diagnostic platforms. Continuous processing, tailored bioreactor or purification units, improved delivery systems will enhance product yields, safety and efficacy. ECaPPH will capitalize on unique capacity in analytical technologies, data science and AI available in Eastern Canada to optimize and integrate bioprocessing pipelines.

4. CLINICAL TRIALS

The ECaPPH ecosystem is internationally recognized for its capacity to organize and lead clinical trials. Through its entire network of clinical research units, Hub members regularly run investigator-initiated trials as well as engage with industry to conduct phase I-IV trials and lead investigator-initiated trials. This expertise was pivotal in commercialization of the only

vaccine made in Quebec recently approved by Heath Canada, Covifenz™ , or in the first phase 1 vaccine clinical study to prevent Zika infections, as well as evaluation of several Canadian pandemic candidates. CIRN also has subnetworks that specialize in AEFI surveillance and evaluation, economic analysis and modelling, and social impacts. Clinical trial procedures are evolving. For example, the SARS-CoV-2 pandemic provided an opportunity to develop **a digital platform for conducting virtual clinical trials** that do not require the same intensity of in-person visits. This platform has the potential to transform the traditional clinical trial paradigm. The use of such new technologies in an integrated, patient-centered approach allows patients to participate in clinical trials from the comfort of their own homes, while reducing the risk of disease transmission. This important paradigm shift will facilitate recruitment, retention and follow-up of participants while testing potential therapies. Aimed at transforming the clinical trial environment, this new platform has the potential to make ECaPPH a world leader while accelerating value creation for our life sciences ecosystem, patients and healthcare system. We are aware of the ongoing CBRF-related Clinical Trial Fund competition and have been in contact with a number of key stakeholders. ECaPPH will create linkages with these efforts so that clinical trials can be done under optimal conditions by trained staff.

5. COMMERCIALIZATION OF DISCOVERIES

Canadian science is competitive internationally in producing high quality results published in prestigious journals. However, we have not met our potential in translation of our discoveries into actual marketed products. Indeed, we need an ecosystem for pandemic preparedness that can integrate the various steps of the discovery pipeline, from pathogen identification, creation of diagnostic, preventive, or therapeutic entities and production for pre-clinical and human trials. Several barriers have been identified in the past 10 years and more specifically during the last pandemic. A known barrier is the transition from preclinical to clinical studies. During the pandemic, it was very difficult in Eastern Canada to move potential drug candidates forward from discovery to phase 1 clinical trials due to lack of biomanufacturing sites to produce investigational product. Indeed, ECaPPH teams developed several candidate therapies and demonstrated their efficacy in early clinical evaluation, but proponents were unable to interest venture capitalists or Angel investors. While several discoveries made in academic laboratories showed considerable promise, few advanced to the point of readiness for submission to regulators.

Lack of knowledge of transfer mechanisms and entrepreneurial skill in the academic sector are contributors in failure to translate discoveries into products. ECaPPH includes partners specialized in valorization and commercialization who will work in a coordinated manner to transform basic discoveries into therapeutics. ECaPPH includes a Network of college centres for the transfer of technologies and innovative social practices (CCTT) that can achieve transfer of innovative processes, methods, practices and products, while contributing to development of a highly skilled workforce. Thanks to the diversity of cutting-edge expertise in innovation and applied research, CCTTs are key players in national strategies and socio-economic development of Quebec and Canada. Building on two major Centre of Excellence in Research and Commercialization, ECaPPH will not only be positioned to support projects, but also to help establish partnerships with large pharmaceutical companies, small biotechs or future start-ups. Moreover, through strategic partnerships with industry, ECaPPH will launch training programs **specifically focused on entrepreneurship** for academics, making them more qualified to deal with industrial and business partners. ECaPPH will be proactive in engaging in early discussions with investigators to recognize upstream discoveries that could have promise for IP and further development.

6. FACILITATE COLLABORATION WITH GOVERNMENTAL ORGANIZATIONS AND POLICY MAKERS

Having pandemic pipelines primed is a crucial early step. However, if information about discoveries ready for adoption never reaches decision and policy makers, caregivers who will use them and patients that accept them, these efforts may be in vain. One of the main roles for ECaPPH will be to build strong links and communication channels with the other CBRF Hubs, local, provincial and national public health agencies, Health Canada and provincial entities dealing with coordinating the supply chain with the federal government. For our early detection and global surveillance theme (section 1) in particular, the Hub

will need close collaboration with public health authorities. ECaPPH includes a critical mass of experts in regulatory processes for new therapeutics and interventions, including nucleic acid-derived products. With current and new partners, we are well positioned to ensure that health authorities participate in identifying research and development needs, and are aware of progress through a robust knowledge translation process. ECaPPH's coordinating role will focus on creating strong links between institutions, industry, government, and the public to ensure success of our overall strategy and future projects. In addition, it is important to mention that ECaPPH partners have strong links in countries, such as Brazil, South Africa, and India, some of which are producers of generics/biosimilars and notably, are also among the most important potential points of origin of emerging infections. We strongly believe that Canadian hubs have to be connected with the international community: pandemics do not respect borders. Indeed, G7 members are forming 'Bioclusters', 'Biomanufacturing Hubs', or 'Institutes of Biomanufacturing' and ECaPPH will build links with these initiatives hence recognizing international interdependence.

7. ENSURING EXPERTISE FOR COMMUNICATION WITH THE PUBLIC TO ENSURE ADOPTION

The COVID-19 pandemic provided an unprecedented communication challenge for government officials and public health authorities due to rapidly evolving knowledge and a background of uncertainty. While scientific-based information should lead communication with the public, we recognize that scientific communication, notably in social media, is an emerging area of expertise. Preventing and dealing with vaccine hesitancy for example, is identified as a known global threat. Learning how to educate different populations and provide a culturally relevant information are essential in a pandemic. Having a large stock of vaccine is useless if a large segment of the population refuses to accept them. ECaPPH members have expertise in vaccine hesitancy and will develop an inclusive communication plan for outreach to the general public and to communities less likely to adopt new treatments. For example, ECaPPH will develop and evaluate "citizen science" to increase the level of outreach. The Hub will develop digital applications to engage a broad public in the analysis of data to enhance the speed and accuracy of data, empowering participants and improving public trust. Some citizen science projects could involve gamification. A good example of this is Borderlands Science in which users play puzzles that represent microbial RNA sequences. The goal is to help ML-AI iron out errors when organizing and analyzing large quantities of sequences, which serve to build a higher-quality body of data that researchers can use to develop novel health or wellness treatments. Other projects have developed applications to learn more about how the COVID-19 pandemic is affecting peoples' way of life including short and long-term impacts on physical, social, mental, and behavioral health and well-being which is part of the monitoring process.

8. EVALUATION AND LONG-TERM MONITORING OF NEW VACCINES AND THERAPEUTICS

The Canadian National Vaccine Safety (CANVAS) Network of the Canadian Immunization Research Network (CIRN) is a national platform that monitors vaccine safety after vaccines are approved for use. The network is monitoring the safety of the new vaccines in Canada using a web-based survey. Other CIRN networks conduct hospital-based surveillance for AEFI and rapid evaluation of efficacy and AEFI using existing databases. Specific ECaPPH members are key leaders in this network. The ECaPPH will secure its involvement with the federal structures in charge of new vaccines and therapeutics such as the Drug Safety and Effectiveness Network (DSEN) to inform public health, the researchers and the public.

9. ENSURING RELEVANT TRAINING FOR HQP INCLUDING SKILLED TECHNICIANS

Many biopharmaceutical companies underwent global restructuring to consolidate operations, which meant moving assets beyond Canada. As a result, we became increasingly reliant on vaccine and therapeutic imports from countries that had the capacity to produce them. Biomanufacturing is more than just processes, equipment, and end products — it is also skilled workers. Canada faces a huge talent shortage. BioTalent Canada's 2021 National Report predicts that Canada's bioeconomy needs 65,000 jobs by 2029, this includes 16,140 biomanufacturing workers and 5,160 in bio-health manufacturing alone. At

the current pace, only 25% of the available roles will be filled. ECaPPH will ensure that new skills and HQP are aligned with significant investments being put into this sector and that these efforts will be sustainable. The need for talent in cGMP is immediate. The creation of relevant content and accessibility to **upskilling/reskilling for current employees** is crucial to redeploy trained talent. Attracting talents is important to supply a pool of employees for innovative new companies and strategic sectors in Canada. Despite the global need to recruit talents with interdisciplinary backgrounds, recruitment into training programs is difficult. Public outreach at early phases of training is needed, and a development pipeline must be established from high-school to college/technical training and beyond to universities. University trainees currently receive little-to-no hands-on training or opportunities to work in an industry context to fully grasp career opportunities. Concepts related to regulatory environments, equity of access, or ethics in the pharmaceutical field are often not taught. A highly interdisciplinary mindset and a shared language are needed by trainees. Many programs are not adapted to provide sufficient biology background to engineers, or engineering background to biologists. Canada must compete with a global demand for talent in an increasingly competitive HQP environment.

ECaPPH will promote shared programs and student mobility, and track such efforts across settings. Courses with common curricula between different universities, recognized across institutions, will be supported. Theoretical and hands-on training covering all aspects of bioprocessing with relevant expression platforms (cell-free, bacteria, yeast, mammalian cells) and products will be developed. A repertoire of teaching infrastructure will be created to exploit institutional strengths, create synergies, improve access and communication between CEGEPs, universities and industries. ECaPPH is the perfect vehicle to create stronger ties between existing programs through coordination, and to foster interactions between students at different levels of training. These programs should also consider the needs of continuous training and career reorientation for HQP already in the workforce. All programs should be interdisciplinary and include a significant course component on regulation of clinical-grade manufacturing, ethics and intellectual property considerations, equity of access and bioeconomics. All trainees should have opportunities for significant interaction with industry, national resources or other operational centers through internships, co-op programs or collaborative research projects.

In summary we propose an ECaPPH that will shape a multidisciplinary and intersectoral ecosystem that will prepare Canada for a swifter and more impactful response during the next pandemics. This will be achieved by state-of-the-art research and development within the remit of the Tri-Council that will lead to countermeasures and social innovations invented and produced in Canada that will impact our response to a pandemic. This will need close networking with public health authorities, policy makers, academia and training institutions, and bio-industries of varying size that will constitute this ecosystem. ECaPPH will be connected with the efforts of the other CBRF-funded hubs and with international hubs with similar goals. In the context of labor scarcity, the Hub will contribute to the critical endeavor of training a new generation of scientists, sensitive to diversity and inclusion issues, that have this coveted multidisciplinary expertise, filling a critical gap in the industry and academia locally and internationally.