### Imperial College London

Future Vaccine Manufacturing Research Hub

# Contents

OVERVIEW FROM FVMR HUB DIRECTOR, PROFESSOR ROBIN SHATTOCK	3
LOWER AND MIDDLE-INCOME COUNTRY PARTNERS	5
MSD Wellcome Trust Hilleman Laboratories – India	5
Vabiotech – Vietnam	5
Uganda Viral Research Institute – Uganda	6
Aimei Hissen Vaccine (Dalian) Co., Ltd. – China	7
Incepta – Bangladesh	8
GlaxoSmithKline – Italy	8
Developing Countries Vaccine Manufacturing Network (DCVMN)	9
RESEARCH	11
FVMR Director, Professor Robin Shattock	11
VACCINE PRODUCTION	12
Professor Gordon Dougan	12
Professor Imre Berger	12
Dr Karen Polizzi	13
Professor Xiao-ning Xu	14
Professor Nicola Stonehouse	14
VACCINE DELIVERY	15
Professor Jason Hallett	15
Professor Molly Stevens	16
Professor Cameron Alexander	16
Professor Harris Makatsoris	17
Dr Rongjun Chen	17
VACCINE MANUFACTURING MODELLING	19
Professor Nilay Shah	19
Dr Cleo Kontoravdi	19
TRANSLATIONAL RESEARCH	20
National Institute for Biological Standards and Control	20
NHS Blood and Transplant	21
Centre for Process Innovation	21
PATENTS	22
TRAINING	23
PUBLICATIONS	25
AWARDS AND HONOURS	26
OUTREACH	27

# Future Vaccine Manufacturing Research (FVMR) Hub

The UK's Department of Health and Social Care formulated the call for Future Vaccine Manufacturing Hubs, administered via the Engineering and Physical Sciences Research Council (EPSRC), in 2017. Imperial College London's FVMR Hub was the first awarded Hub, valued at £10 million, which partners with UK-based institutes as well as vaccine manufacturers in LMICs, such as China, Bangladesh, India, Vietnam and Uganda.

Imperial College London's FVMR Hub is committed towards researching innovative and more costeffective vaccines for populations in lower- and middle-income countries (LMICs). With the project population growth for our globe expected to exponentially increase in the developing world, the projected need of vaccine doses is projected to increase dramatically within the next 10 years (Figure 1) – led by Imperial College London, the FVMR Hub is ideally placed towards supporting the established and emerging vaccine manufacturing processes in the developing world.

Vaccines have indeed saved millions of lives over the last century, though there are still countries in need of better access to effective vaccines and innovative or disruptive new technologies in vaccine manufacturing. The vaccine manufacturing sector in the developing world and patient populations will benefit from successful outcomes from Imperial's FVMR Hub – this Annual Report aims to provide an overview of activities and progress thus far.

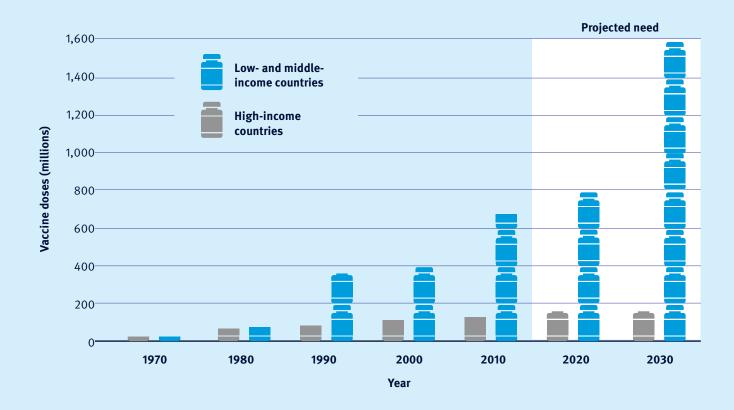


Figure 1. History and projected need for vaccine doses in developing and developed world. Figure adapted from references 32, co-authored by Rino Rappuoli, Chair of the Advisory Board to Imperial's FVMR Hub, published in *Science Translational Medicine* in 2019.



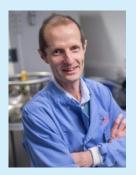
## **Overview**

#### From FVMR Hub Director, Professor Robin Shattock

Vaccines continue to be one of the most important and powerful discoveries and medical innovations in our history, estimated to prevent 2.5 million deaths per year. Aside from access to clean water and good sanitation, vaccines are the best insurance for good societal health, ensuring that humans can be protected against infectious diseases such as measles, mumps, rubella and influenza. Previously resulting in 500,000 deaths per annum, smallpox was eradicated in 1979 due to a worldwide vaccination effort coordinated by the WHO, resulting in annual savings of \$1.35 billion. Vaccinations can lead to other beneficial indirect effects, for example children vaccinated for rubella (German measles) importantly protect against infecting pregnant women, since foetuses are susceptible for being seriously damaged by this virus. Overall, vaccines have directly impacted our health, whilst indirectly benefiting our economic and societal growth. Our species has never been healthier, and this is largely because of successful vaccines.

There are currently numerous emerging infectious diseases, such as Ebola virus, Rift Valley Fever, Zika virus – umbrellaed under the moniker "Disease X", in which responses can be greatly strengthened from the advent and distribution of vaccines. However, standard manufacturing practices are too slow and centralised – we are currently unable to quickly (i.e. within weeks) and aptly (i.e. locally) or efficiently (i.e. without cold chain distribution) deliver vaccines that defend against an outbreak of disease. Our planet is evolving and changing more rapidly than ever: there will be further emerging infectious diseases that will require rapid interventions using vaccines. Disruptive approaches in vaccine manufacturing are needed to create vaccines that can be administered in localised outbreaks or global events, such as influenza pandemics.

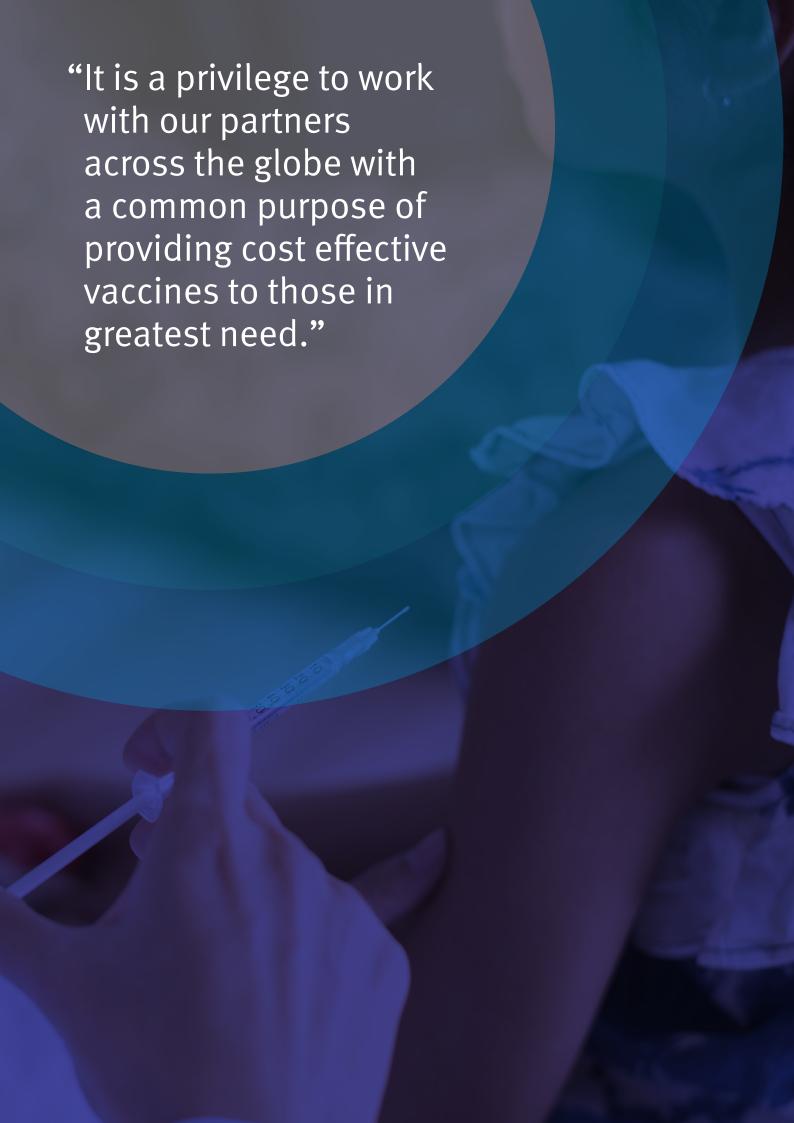
Furthermore, current vaccine manufacturing procedures were honed by practices undertaken during the 1950's through the 1980's, when life expectancy was shorter than the current average of 55-75 years of age. Current lifespans are longer than ever, whilst populations are expanding mostly in developing countries. Also, in developing countries, market drive does not exist to facilitate the establishment of manufacturing facilities as in developed countries, whilst often vaccine needs are driven by medical needs – exemplifying this is how rotavirus vaccine has thus far not been effective in developing countries. Poliomyelitis (polio) cases decreased by over 99% since 1988, but polio remains (65 wild poliovirus (WPV) cases reported thus far from 1 January – 20 August 2019; 33 WPV cases were reported in all of 2018), which is in sharp contrast to when this disease was prominent prior to the 21st century. The creation of manufacturing practices that facilitate long-lasting, effective more rapid, cost-effective solutions towards improving standard manufacturing processes in the developed world and manufacturing needs of developing countries – are needed for the 21st century. Vaccine manufacturing practices need to be updated according to the needs of our species.



Professor Robin Shattock, FVMR Hub Director

"Humans have never been healthier, and this is largely because of successful vaccines."

"Vaccine manufacturing practices need to be updated according to the needs of our society."



# Lower and Middle-**Income Country Partners**



#### INDIA

#### MSD Wellcome Trust Hilleman Laboratories

The WHO¹ estimates that 100,000-120,000 deaths occur each year due to cholera. With an estimated 1.4 billion of the global population at risk and endemic in 51 countries, cholera spreads rapidly and severe outbreaks have been seen recently in countries such as Haiti, Vietnam, and Zimbabwe. Currently, there are three pre-qualified oral cholera vaccines, Dukoral© (Valneva, Canada), Shanthol™ (Shantha Biotechnics Limited, India), and Euvichol® (EuBiologics Co., Republic of Korea). Dukoral© is a killed whole-cell monovalent (O1) vaccine with cholera toxin B subunit.<sup>2</sup> first licensed in Sweden in 1991, whilst both Shanthol™ and Euvichol© are killed modified whole cell bivalent (O1 and 0139) vaccines without the B subunit - thus do not protect against Enterotoxigenic Escherichia coli (ETEC). The implementation of an oral cholera vaccine is a sector of the interventions to control cholera in the WHO's Global Roadmap<sup>3</sup> to end cholera by 2030. Providing cost-effective cholera vaccines towards this end will support our progress towards a WHO Sustainable Development Goal.

The MSD Wellcome Trust Hilleman Laboratories<sup>4</sup> (Hilleman) are located in New Delhi, India. Hilleman comprises a joint funded effort between Merck, Sharp, & Dohme and the

"With an estimated 1.4 billion of the global population at risk and endemic in 51 countries, cholera spreads rapidly and severe outbreaks have been seen recently in countries such as Haiti, Vietnam, and Zimbabwe"

Wellcome Trust, targeting vaccines protecting against diseases in the developing world. With support and collaborations with the FMVR Hub, Hilleman are working towards a cost-effective and more affordable oral inactivated cholera vaccine (Hikojima serotype) that also protects against ETEC (with recombinant cholera toxin B subunit as an active component; heat-labile enterotoxin B is also a component). Hilleman is collaborating with the University of Cambridge and Professor Gordon Dougan's group towards developing antigens. Hilleman also has key collaborations with Imperial College London and Professor Robin Shattock's group to research strategies for manufacturing more stable components, along with Professor Jason Hallett's group to research strategies for manufacturing more stable products, to minimise the influence of cold chain transport.

#### VIETNAM



Our global society is attacked by the influenza virus each year, which has claimed millions of deaths in the past century. Currently, up to 650,000 deaths occur due to seasonal influenza.5 Vaccine-based strategies are encumbered by the influenza virus mutating when it replicates - causing antigenic shift and drift. The WHO coordinates global preparation each year for the next influenza outbreak

and publishes the strains predicted to be prevalent in the coming months, directing the manufacturing of appropriate vaccines. However, such vaccines are currently only 36% effective<sup>6</sup> (2017-8), and the manufacturing protocols are labour- and time-intensive, whilst distribution on a global scale is challenging. The WHO's Global Influenza Strategy 2019-2030 calls for more effective vaccines that

#### 650,000 deaths

occur due to seasonal influenza currently.

would instil public confidence and uptake, especially in LMICs. Influenza shortages can occur, which has been an issue recently in the UK, whilst the threat of the next influenza pandemic increases the need for more proactive strategies for preparedness and more streamlined distribution pipelines. Influenza claimed 100,000-400,000 deaths alone in the last pandemic (2009). Pandemic influenza, which has struck in 1918 (H1N1), 1957 (H2N2), 1968 (H3N2), 1977 (H1N1), and 2009 (H1N1/09), occurs when an epidemic of an influenza virus, transmitted from animals, spreads on a worldwide scale. It is estimated that the next influenza pandemic can claim up to 30 million deaths within 6 months.8 Current influenza vaccines in the northern hemisphere are designed to protect against H1N1 and H3N2 type A strains (along with up to 2 B strains), whilst the next pandemic is suspected to be a highly pathogenic H5 or H7 type A virus9 transmissible by humans, though fortunately, these strains currently do not transmit efficiently amongst mammals. To better protect our society against regularly circulating influenza viruses as well as to be prepared against the next pandemic, new and disruptive platform technologies capable of more efficiently manufacturing influenza vaccines are greatly needed.

Vabiotech<sup>10</sup> is located in Hanoi, Vietnam. With a strong history in developing cholera vaccines, Vabiotech currently provides vaccines for cholera (mORCVAX), Japanese Encephalitis (JEVAX© and JEBEVAX), Hepatitis A (HAVAX©) and Hepatitis B (Gene-HBvax), as some examples. Within the FVMR Hub, and in collaboration with Professor Imre Berger from the University of Bristol, Vabiotech is researching the baculovirusbased manufacturing of influenza virus-like particles (VLPs) in insect cell culture. Berger's lab invented MultiBac, 11 which is tailored for heterologous multigene transfer and multiprotein complex production - suitable for VLP and vaccine manufacturing. MultiBac delivers customised baculovirions and DNA cargo to mammalian cells and tissues. Berger has used MultiBac to produce recombinant VLPs based on the M1 capsid from the influenza H1N1 strain that lack genetic contact, thereby enhancing their safety profile. MultiBac may be applied to multiple disease targets. Vabiotech staff have seconded in Berger's labs in Bristol in 2019, whilst the FVMR Hub is supporting the technology transfer of the MultiBac technology to Vabiotech, in Hanoi, Vietnam.

#### UGANDA



#### Uganda Viral Research Institute

Africa is in urgent need of more effective and readily available vaccines. Since 2000, the Global Alliance for Vaccines and Immunizations (GAVI) has performed exceptionally well in improving vaccine availability in several African countries by supporting importation. However, there are questions regarding financial stability and sustainability once countries graduate from the GAVI programme. 12 Local production of vaccines in Africa could transform this situation and enable vaccines that can be better tailored for local threats, distributed locally and create faster responses to epidemics and outbreaks. This need is especially acute as the population of Africa is increasing at a high rate: 2.9 billion people are expected in Africa by 2100. Currently, there are but a few vaccine manufacturing companies in Africa:13 Institut Pasteur de Dakar14 (Senegal) produces pre-qualified yellow fever vaccine; Vacsera<sup>15</sup> (Egypt) manufactures BCG, DTP, typhoid and cholera vaccines; the Biovac<sup>16</sup> Institute (South Africa) manufactures a range of vaccines; Institute Pasteur de Tunis<sup>17</sup> (Tunisia) has very limited BCG and rabies; and the Ethiopian Public Health Institute (Ethiopia) has provided vaccines for typhoid and rabies for some years.18 Ethiopia

exemplifies issues faced by African countries: this country is currently being supported by GAVI, whilst the government has committed a \$50 million investment and \$100 million further donations have been directed towards vaccine supplies. However, the cost of manufacturing vaccines in Ethiopia is expected to triple following the departure of GAVI support. Ethiopia is also developing local pharmaceutical manufacturing capacity,19 which aims to meet 50% of local needs for essential medicines through local manufacturing. Significant efforts are needed for this to be realised based on traditional vaccine manufacturing processes. Despite some positive momentum and support for local vaccine production within Africa, there are deadly epidemics, such as the 2014 Ebola virus outbreak

"Local production of vaccines in Africa could transform this situation and enable vaccines that can be better tailored for local threats, distributed locally and create faster responses to epidemics and outbreaks."

that claimed more than 11,000 lives, the polio virus is still existent in Nigeria, and other recent outbreaks have been seen for diseases without licensed vaccines, such as Lassa fever, Rift valley fever and Zika virus. Drastic measures and new strategies are urgently required to support the vaccine needs of a growing African population.

The Uganda Viral Research Institute (UVRI) is located in Uganda. In partnership with the FVMR Hub, the UVRI is collaborating with Professor Robin Shattock's group, who is researching an innovative platform technology based on RNA. Nucleic acid-based vaccines represent a next generation option20 for vaccines as they exploit the body as a reactor to produce antigens and subsequently antibodies for protection, whilst they are completely synthetic and may be easily tailored for a particular antigen. DNA vaccines have shown disappointing results in the clinic. RNA vaccines show enormous potential as they avoid the need for nucleus penetration, have self-adjuvant properties, whilst they have no risk of integration within the host genome. RNA can be deployed with self-replicating potential, which "RNA vaccines show enormous potential as they avoid the need for nucleus penetration, have self-adjuvant properties, whilst they have no risk of integration within the host genome."

results in exponentially more antigen production, therefore lowering the required dosage. The avoidance of egg- or cell-based production offers a less restrictive and potentially more open regulatory landscape for GMP production procedures, therefore potentially enabling RNAproducing facilities in less resource-available settings. Professor Shattock is training staff from the UVRI on the production of RNA designed to produce the antigen for Rift Valley Fever, whilst collaborations are ongoing towards the blueprint and establishment of a GMP-like RNA production facility in Uganda. GMP-like production of RNA is being trialled by FVMR Hub partner CBC. This work stream aims to implement this innovative and disruptive technology within Uganda.

#### CHINA



#### Aimei Hissen Vaccine (Dalian) Co., Ltd.

Hand, foot and mouth disease (HFMD) is rampant in China, whilst outbreaks have occurred across Asia, mostly affecting children. In July 2018 alone, 377,629 cases<sup>21</sup> in China were reported. Caused predominantly by Coxsackievirus A16 or enterovirus 71 (EV71), HFMD pressures public healthcare infrastructures due to parents requiring sick leave to care for afflicted children, whilst meningitis or encephalitis can arise in rare cases. There are three licensed vaccines in China, 22 such as a formalin-inactivated monovalent EV71 vaccine from Sinovac Biotech Ltd., which shows excellent protection for EV71<sup>23</sup> but none for Coxsackievirus A16,24 and others from Beijing Vigoo Biological Co., Ltd. and the Institute of Medical Biology, Chinese Academy of Medical Science (CAMS). That none of the major multinational vaccine companies, such as GlaxoSmithKline, Merck Sharp & Dohme and Sanofi Paster,25 is pursuing R&D of an EV71 vaccine exemplifies why further investment and international Hub-based support for vaccine development in LMICs. The EV71 vaccine from CAMS is produced using human diploid cells,26 and alternate formulations, such as VLPs, and production components, such as yeast, can provide substantial benefits towards the currently used labour- and time-intensive protocols. Yeast is already used to manufacture

VLP-based vaccines for hepatitis B and human papillomavirus, and it offers advantages such as high yields and decreased cost compared with diploid cell manufacturing methods. Yeast-derived VLP administration abolishes the potential for disease-carrying burdens and can offer cross protection against infection from EV71 as well as Coxsackievirus strains.

Within the FVMR Hub, Aimei Hissen Vaccine (Dalian) Co., Ltd. in China is partnering with Professors Xiao-ning Xu. Xu is generating yeast platforms using *Saccharomyces cerevisiae* strains to generate EV71 and Coxsackievirus VLPs. Chimeric VLPs targeting surface antigens for Hepatitis B are also being pursued. Professor Xu's VLP candidates will be optimised and validated and then trialled in the GMP facilities available within Aimei Hissen Vaccine (Dalian) Co., Ltd. in China. Xu is also pursuing VLP-based candidates against chikungunya virus, as no vaccine against chikungunya currently exists.

"Hand, foot and mouth disease (HFMD) is rampant in China, whilst outbreaks have occurred across Asia, mostly affecting children."

#### **BANGLADESH**



#### Incepta

Human papillomavirus (HPV) causes cervical cancer, which leads to approximately 275,000 annual deaths, a majority of which occur in less developed regions, along with other genital and oropharyngeal cancers. HPV types 16 and 18 together are responsible for approximately 70% of cervical cancer cases, <sup>27</sup> and there are currently three HPV vaccines available protective against these two types: Cervarix (HPV16/18), Gardasil (HPV6/11/16/18) and Gardasil-9 (HPV6/11/16/18/31/45/52/58). These vaccines are based on VLPs comprising an array of 360 copies of the L1 major capsid protein. <sup>28</sup> Multivalent VLP-based vaccines induce



"The FVMR Hub is committed towards the manufacturing of innovative vaccines using the highest quality approaches across the development pipeline."

impressive immunological memory, irrespective of the addition of TLF agonist adjuncts. VLP size is thought to be critical in determining the resultant antibody half-lives, and this is best controlled in the purification steps of the vaccine manufacturing processes. The FVMR Hub is committed towards the manufacturing of innovative vaccines using the highest quality approaches across the development pipeline.

Incepta Vaccine is located in Bangladesh. Incepta has a broad span of vaccines in their portfolio, including rabies, influenza, measles, rubella, tetanus, typhoid, hepatitis B, and hepatitis A; these vaccines are distributed within Bangladesh. In collaboration with Dr Karen Polizzi at Imperial College London, Incepta staff are being trained in the use of yeast (i.e. Pichia pastoris) towards the extracellular production of VLPs for HPV and Hepatitis E. This collaboration is also researching whether yeast can be used to extracellularly produce VLPs for chikungunya, which is endemic or epidemic in nearly 40 countries.29 With Dr Polizzi, Incepta also aims to produce rabies glycoprotein using yeast.

#### ITALY



#### GlaxoSmithKline

GlaxoSmithKline (GSK) represents one of the major multinational vaccine manufacturers and is responsible for the manufacturing and distribution of a number of vaccines that have benefited millions and saved numerous lives over the past several decades. In partnership with the FVMR Hub, GSK is committing resources into researching and developing innovative vaccine production procedures that enable platform technologies, focusing on the Gramnegative generalised modules for membrane

"Platform technologies amenable to retailoring for different diseases are needed to allow approaches that are not completely dependent on centralised manufacturing sites."

antigens (GMMA) technology, which is featured as one of the "vaccines for tomorrow".<sup>30</sup> Platform technologies amenable to retailoring for different diseases are needed to allow approaches that are not completely dependent on centralised manufacturing sites. An example of this is how a viral vector approved for one disease may be exploited for another based on its established safety information or profiles. With their high immunogenicity, effectiveness, low reactogenicity, self-adjuvant properties, high safety profiles and low cost, GMMA-based vaccines are touted as one of the lowest risk<sup>31</sup> and highest potential<sup>32</sup> next generation class.

GMMA are created by deleting *gna33* in meningococcus or *tolR* in *Shigella sonnei* and *Salmonella*, which enhances native outer-

membrane vesicle production. Within the FVMR Hub, GSK is exploring GMMA for the design of multicomponent vaccines. GMMA can be easily manipulated to display heterologous antigens on their surface. GSK is also collaborating with Professor Robin Shattock towards a rabies virus glycoprotein to test its conjugation with GMMA. GMMA vaccines have shown excellent results in clinical studies – they are poised for downstream development – whilst Hub member Dr Francesca Micoli from GSK (and colleagues) has shown bivalent GMMA confer equal or enhanced immunogenicity compared with traditional glycoconjugates for non-typhoidal Salmonella.<sup>33</sup> Further support is provided within

the FVMR Hub from Dr Cleo Kontovradi, who has generated cost analyses and Quality-by-Design (QbD) maps for GMMA production within GSK, along with Dr Rongjun Chen, who is researching GMMA reformulations. In collaboration with NIBSC, GSK is working on the standardisation of release/stability assays and reference standards for GMMA based vaccines. Within the Hub, GSK is targeting advanced GMMA vaccine candidates for diseases such as non-typhoidal *Salmonella* or ETEC/*Shigella*, which are ubiquitous across the globe<sup>34</sup> and require innovative vaccine-based approaches due to increasingly prevalent antimicrobial resistant strains.

#### ITALY



#### Developing Countries Vaccine Manufacturing Network (DCVMN)

There are substantial challenges facing vaccine distribution within developing countries. The developing world is most in need of more, better vaccines, and it is forecast to incur an exponentially higher population growth in the next 100 years with respect to the developed world. The supply of effective vaccines, which are currently in need of end-to-end cold-chain distribution methods, cannot be reliably sustained for the demographics most in need of protection. The world has been near to polio eradication for decades, and this disease is still existent. Vaccine hesitancy is considered a serious challenge for the developed world,35 whilst vaccine distribution and availability is the challenge to overcome for the developing world. Innovative technologies, disruptive distribution protocols, and improved manufacturing capabilities for facilities in developed countries is a noble though challenging set of goals being addressed by the FVMR Hub.

The Developing Countries Vaccine Manufacturing Network (DCVMN) currently has 44 member companies from developing countries. The FVMR Hub participated in two DCVMN Executive "There are substantial challenges facing vaccine distribution within developing countries."

Committee meetings, whilst the FVMR Hub had symposia organised for the DCVMN Annual Meetings in 2018 and 2019), DCVMN has put out calls for its members for funds from the Hub to pay for consultants to improve QC processes, first in 2018 and continued in 2019. DCVMN members are also encouraged to engage with Hub scientists towards improving their manufacturing processes. Supported by FVMR Hub member NIBSC, DCVMN members will be invited to apply for funding to support on-site training within NISBC in the UK, where a team is trained on QC assays, in 2020, to ensure that knowledge transfer is ensured: this call was introduced first at a DCVMN meeting in Hyderabad, India in 2019. The Hub is also supporting the DCVMN to address supply chain issues that developing country manufacturers, by participating in a workshop on the topic in Geneva in June 2019. The Hub also supports e-learning training of DCVMN members.



### Research

#### FVMR Director, Professor Robin Shattock



Director of the FVMR Hub, Professor Robin Shattock has a strong track record of researching innovative vaccines against a number of targets, such as HIV, Ebola, EV71, Adenovirus, Rabies, and Lassa Fever, prevalent within a developing world setting. Professor Shattock coordinates activities across the Hub, such as activities that focus on researching innovative and disruptive RNA-based vaccine candidates. Within the FVMR Hub, RNAbased candidates are on the lower technology readiness level (TRL) and successful candidates require pre-clinical data and clinical trials for their progression and development support. Shattock has conducted several Phase I clinical trials, funded from elsewhere. His research has revealed important aspects of the roles of adjuvants<sup>36 37 38</sup> and administration routes<sup>39 40</sup> for HIV vaccine candidates, and proved the scaleable manufacturing of griffithsin as an inhibitor of HIV-1 entry, by modifying the tobacco mosaic virus and incorporating the griffithsin gene in more than 9,300 tobacco plants.41

Shattock is convinced that RNA-based vaccines are poised to become the next generation class of vaccines against viral infections. Traditionally, viral vaccine manufacturing relies on egg or cell culture methods to retrieve attenuated (weakened) or inactivated (dead) viruses. By attempting to transform a patient's body into a bioreactor that produces antigens, nucleic acid-based vaccines can transform the manufacturing features used in the production of traditional vaccines, as they are completely synthetic and can be produced within a week. DNA-based vaccines showed promise in the 1990's with the aim of encoding the protein producing machinery intracellularly, though there are several drawbacks for DNA-based vaccines, such as potential incorporation within the host genome. RNA-based vaccines are considered a safer alternative in that they are unable of incorporating within the host genome. Additionally, RNA functionality requires entry into the cytosol rather than the nucleus (as required by DNA vaccines), which is protected by the nuclear envelope.

Shattock has been pursuing replicating RNAbased vaccines, or "replicons", which encode the antigen as well as the capability to produce more RNA. This replicating effect can reduce the amounts administered when compared with nonreplicating mRNA vaccines, thereby increasing safety profiles and cost-effectiveness. Moreover, this may be helpful in balancing the selfadjuvant nature of RNA. Within the FVMR Hub, Shattock is pursuing replicon-based vaccine candidates for a range of diseases, with the goal of validating GMP-like manufacturing protocols with UK-based partner CBC and establishing GMP-like manufacturing facilities in Uganda, in partnership with the UVRI. A staff member from the UVRI in Uganda is currently receiving training and performing his PhD studies within Professor Shattock's laboratories.

"Shattock has been pursuing replicating RNA-based vaccines, or "replicons", which encode the antigen as well as the capability to produce more RNA."

## **Vaccine Production**

#### Professor Gordon Dougan



Professor Gordon Dougan is currently Honorary Professor at the University of Cambridge and Head of Pathogen Research as well as a member of the Board of Management at the Wellcome

Trust Sanger Institute. Dougan is contributing within the FVMR Hub by collaborating with the Hilleman Labs in New Delhi, India. Dougan researches the genetic analyses of host-pathogen interactions during infection, whilst he has provided analyses for the seventh pandemic of cholera<sup>42</sup> as well as human invasive Salmonella Typhimurium pathovariants in sub-Saharan Africa.<sup>43</sup>

Within the FVMR Hub and in close collaboration with Hilleman, Dougan is developing novel cholera-E. coli candidate conjugate vaccines. Dougan has sequenced the genomes of both the Hikojima Vibrio cholerae vaccine carrier and Enterotoxigenic E. coli to produce novel conjugate vaccines, whilst he is also pursuing polysaccharide antigens to several meningococcal capsular types - particularly in conjugation with the meningococcal surface protein factor H-binding protein. Dougan is also researching innovative protocols towards antigen production against typhoid and paratyphoid infections. Professor Dougan's lab also performs RNAseg analyses to support efforts within the Hub.

"Within the FVMR Hub and in close collaboration with Hilleman, Dougan is developing novel cholera-E. coli candidate conjugate vaccines."

#### Professor Imre Berger



For many products, vaccine production relies on protocols featuring mammalian cell culture. For example, MMR vaccines are based on human diploid cells to retrieve attenuated virions.

Mammalian-based cell culture has several drawbacks such as slow doubling times and high passage numbers, which can be circumvented with the use of insect cells. Baculovirus is a successful DNA-based vector used to infect and generate virions from insect cells. FluBlok© is manufactured using baculovirus-insect cell expression systems. baculovirus-based manufacturing of influenza virus-like particles (VLPs) in insect cell culture. Professor Imre Berger's MultiBac, 12 which delivers customised baculovirions and DNA cargo to mammalian cells and is tailored for heterologous multigene transfer and multi-protein complex production. Berger has also created ADDomer, an adenovirus-based scaffold that can produce high yields of various protein targets.

Professor Imre Berger is pursuing technology transfer of MultiBac with partners Vabiotech in Hanoi, Vietnam. Vabiotech currently do not have established facilities for insect culture with exploitation of the MultiBac technologies. The successful implementation of this technology within an LMIC will represent a major goal of the FVMR Hub, which is to research and implement innovative technologies amenable for LMIC vaccine manufacturers. Vabiotech are focusing efforts on exploiting the MultiBac system to produce influenza vaccines - Vabiotech staff seconded in the Berger labs in 2019 and are aiming towards technology transfer. MultiBac and ADDomer have increased TLR levels with respect to RNA technology. For example, ADDomer has been graded as a promising emergent vaccine production technology whilst Berger is also co-founder of spin-out Imophoron, which has rights for the ADDomer technology.

"Professor Imre
Berger is pursuing
technology
transfer of
MultiBac
with partners
Vabiotech in
Hanoi, Vietnam."

"Dr Polizzi has expertise in exploiting Pichia pastoris as a promising class of yeast capable of reaching extremely high cell densities and producing high yields."

#### Dr Karen Polizzi



Yeast are an exciting potential source for vaccine production. They are empowered with lower risk for contamination (i.e. virusfree) and rapid production fermentation periods: yeast-

produced VLP-based vaccines are established and available (e.g. for Hepatitis B and HPV). However, production levels are typically lower than other production routes and human-like glycosylation has not been established at production scale. Dr Polizzi has expertise in exploiting Pichia pastoris as a promising class of yeast capable of reaching extremely high cell densities and producing high yields.<sup>44</sup>

Within the FVMR Hub, Polizzi is researching yeast-based platforms towards the production of rabies virus glycoprotein, engineering yeast capable of producing fully humanised glycoproteins as well as CRISPR-based methods of generating yeast capable of enhanced protein expression. Polizzi is also collaborating with Incepta (Bangladesh) by training and guiding their research staff towards using yeast to produce VLPs for HPV and Hepatitis E as well as carrier proteins for polysaccharide conjugate vaccines. Incepta staff seconded in the Polizzi labs at Imperial College London in 2019 and are aiming towards technology transfer of yeast-based vaccine production technologies to their site in Bangladesh.



"One of the most promising outputs of yeast as vaccine-producing platforms is VLPs."

#### Professor Xiao-ning Xu



Professor Xiao-ning Xu is Chair in Human Immunology within the Department of Medicine and leads the Centre for Immunology and Vaccinology<sup>45</sup> at Imperial College London. Xu was Head of

Novartis Vaccines Research China in Novartis Vaccines & Diagnostics, based in Shanghai, China. Xu has expertise in vaccine production in an industrial setting and is expert particularly in host-immune responses.<sup>46</sup>

One of the most promising outputs of yeast as vaccine-producing platforms is VLPs. VLP-vaccines can induce extremely high immunities against infections such as Hepatitis A and Japanese Encephalitis, in some cases life-long protection after a single immunisation. Yeast are attractive for a number of reasons, such as amenable manufacturing costs and lower risks. Within the FVMR Hub, Xu is pursuing yeast-based platforms to produce VLPs with improved post-translational modifications. The two vaccine targets being researched are against chikungunya virus and EV71, which causes HFMD. Within the FVMR Hub, Xu is partnering with Aimei Hissen Vaccine (Dalian) Co., Ltd. in China towards the validation of the yeast-based production of VLPs in GMPlike conditions. Mid-scale production (20L) is currently being targeted, whilst longer-term plans include larger-scale production within the Chinese laboratories. The technology transfer here is being supported via secondments of Aimei Hissen staff within the Xu laboratories at Imperial College London.

#### Professor Nicola Stonehouse



The FVMR Hub is committed towards supporting efforts in improved vaccine manufacturing methods in LMICs, improved UK-based research and development towards such technology transfers,

as well as supporting UK-based research in innovative vaccine manufacturing. The FVMR Hub is open to new members whose research aims align with Hub goals. In 2018, the FVMR Hub partnered with the Innovate UK's Knowledge Transfer Network (KTN), which coordinated a launch event for UK-based potential partners in May 2018 at Imperial College London. A wide range of interest in the FVMR Hub was received as 60 members from the manufacturing committee and UK academics attended and expressed interest for further engagement.

Professor Nicola Stonehouse, Professor in Molecular Virology from the University of Leeds, engages with the Hub and particularly in partnering with the Centre for Process Innovation (CPI). Stonehouse and her colleague Dave Rowlands lead a WHO-funded consortium (together with the Universities of Oxford, Reading, Florida, NIBSC, JIC, Norwich and the Pirbright Institute) researching novel genetically-modified VLP-based vaccines, such as against EV71 and polio. Stonehouse is currently collaborating with CPI to perform the upstream manufacturing of yeast-based VLPs. Advances in this research aims to inform improved vaccines against polio.

# **Vaccine Delivery**

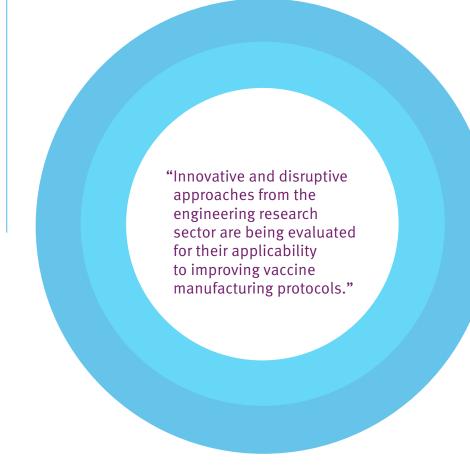
#### Professor Jason Hallett



The currently established cold chain-dependent distribution pipeline for vaccines results in massive costs, higher risks and significant barriers hindering the more efficient and widespread availability of

vaccines. Liabilities for ensuring the transport of cold-chain dependent goods lie with exporting manufacturers until a certain point, whilst risk handover to different national networks may result in mismatched quality profiles. There is currently no cost-based incentive for national distributors to adhere to often stringent requirements put forth by centralised production facilities once the goods are received by national customs. Oftentimes, vaccines cannot be distributed to remote demographics most in need as a cold-chain distribution pipeline is not in place or is inadequate. Innovative and disruptive approaches from the engineering research sector are being evaluated for their applicability to improving vaccine manufacturing protocols.

Professor Jason Hallett of Imperial College London is researching innovative ways to modify vaccine components to increase their stability without altering or decreasing their immunogenic activities. Hallett has developed methods of solubilising and stabilising enzymes, for applications in treating biomass materials,<sup>47</sup> with exciting potential applications in vaccine production. In a recent example, as published in *Nature Chemistry*, <sup>48</sup> the Hallett group chemically modified glucosidase and achieved thermal stability of up to 137 °C. Strategies based on this are being applied to modify ingredients in vaccine formulations to improve their stability profiles and prolong their shelf-lives. Hallett presented this new approach to vaccine production at the World Economic Forum in Davos, Switzerland in January 2019. This engineering approach exemplifies the multidisciplinary environment within the FVMR Hub. Hallett's group is collaborating with Professor Robin Shattock towards stabilising RNA-based vaccine candidates.



"RNA complexed with more effective cationic polymers can achieve much higher entry to cells to achieve cytosolic activation and processing of RNA, resulting in reliable protein expression."

#### **Professor Molly Stevens**



Professor Molly Stevens is currently Professor of Biomedical Materials and Regenerative Medicine and the Research Director for Biomedical Material Sciences at Imperial College

London. Stevens researches a broad range of research faculties, including engineering, chemistry, biology, physics and medicine. Her multidisciplinary approach to research has resulted in paradigm shifts in areas such as cardiovascular calcification aetiology, 49 nanomaterials 50 and characterisation, 51 enzyme biosensing and detection 52 and mHealth, 53 with publications in *Science* and *Nature* family journals. Stevens also pursues research in polymeric materials for applications in biomedicine. Recently, a functionalised polymer-based template achieved mitigation of inflammation and fibrosis *in vivo*. 54

Polymers are ideal candidate carriers to achieve enhanced delivery of sensitive vaccine components. Polyethylene imine (PEI), a cationic polymer, is the most common class of materials capable of intracellular delivery, though PEI can induce a cytotoxic response. Cationic polymers shield the repulsive effects from the negatively charged cell membrane in proximity with negatively charged agents, such as RNA moieties, though less cytotoxic polycationic materials are needed. RNA complexed with more effective cationic polymers can achieve much higher entry to cells to achieve cytosolic activation and processing of RNA, resulting in reliable protein expression. In collaboration with Professor Shattock, Professor Stevens is researching innovative cationic polymers to form RNA-based nanoparticle complexes that can be formulated as a new vaccine component.

#### Professor Cameron Alexander



Professor Cameron Alexander is Professor of Polymer Therapeutics at the University of Nottingham. Alexander has researched polymers towards a number of innovative applications. For

example, as published in *Nature Materials*, Alexander created a polymer class synthesised as instructed by proximal bacteria, creating a self-reporting system enabling improved diagnostic assays,<sup>55</sup> whilst another example of polymers is reported to sequester quorumsensing bacteria, published in *Nature Chemistry*.<sup>56</sup> Alexander researches polymer-based materials across a broad range of classes for a myriad of applications, including gene delivery, therapeutics and regenerative medicine.

Within the Future Vaccine Manufacturing Research Hub, Alexander is collaborating with Professor Robin Shattock and Professor Molly Stevens towards innovative polymerbased carriers capable of transfection levels commensurate with PEI and with improved cytotoxicity profiles, cellular uptake efficiency, better protection from nucleases, increased retention time in blood retention time when injected systemically, whilst these materials are designed to be synthesised and scaled up to GMP conditions. Alexander's team is investigating modifications such as various synthetic conditions, functional handles and freezing conditions towards the optimal polymer carrier candidate(s).

"Alexander's team is investigating modifications such as various synthetic conditions, functional handles and freezing conditions towards the optimal polymer carrier candidate(s)."

"Virus-mimicking nanostructures are being engineering within the Chen labs as candidate carriers for vaccines within the FVMR Hub."

#### Professor Harris Makatsoris



Professor Harris Makatsoris is Professor of Manufacturing Operations in the Sustainable Manufacturing Systems Centre at Cranfield University. Makatsoris has expertise in small-scale local

production technologies, materials sciences, process engineering and manufacturing systems. Makatsoris is researching manufacturing protocols to serve a new niche in the market,57 amenable for implementation in smaller, decentralised vaccine manufacturing facilities. Lab-on-a-chip, small-scale production, continuous or flow processing and modular manufacturing components are revolutionising manufacturing across many sectors. Several manufacturing sectors are facing potential paradigm shifts in manufacturing protocols to create more reliable procedures with fewer batch-to-batch variations. The vaccine manufacturing field needs to consider new manufacturing approaches with such powerful in-line procedures on-hand.

In collaboration with Professor Robin Shattock within the FVMR Hub, Makatsoris is researching in-line monitoring protocols for a modular and automated manufacturing device for RNA components. This research is informing the manufacturing protocols required for large-scale production of RNA as well as potential modular production processes. A comparison of modular and large-scale approaches will unveil the optimum placement for RNA ingredients in vaccine formulations.

#### Dr Rongjun Chen



Dr Rongjun Chen is currently Senior Lecturer at Imperial College London. Chen has expertise in engineering innovative polymers, such as responsive systems, as novel

delivery carriers. The innovative vaccine antigens or RNA components engineered within the Hub require carrier components that protect them from degradation or prolong their circulation whilst maintaining their activity.

Chen has performed research on material classes capable of disrupting membranes by incorporating stimuli-sensitive behaviour, whilst minimising toxicity profiles.58 Liposomes are a successful carrier class to deliver sensitive antigens in vaccine formulations.<sup>59</sup> Chen has reported pH-responsive liposomes<sup>60</sup> that mimic the endosomolytic behaviour of native influenza viral peptides, whilst incorporated cholesterol mimics the viral envelope. Virus-mimicking nanostructures are being engineering within the Chen labs as candidate carriers for vaccines within the FVMR Hub. Chen is collaborating with Professor Robin Shattock towards developing a liposome-carried RNA-based vaccine candidate. Chen is also collaborating with FVMR Hub member GSK towards the incorporation of polymers within GMMA towards enhancing their membrane permeability capabilities.



# Vaccine Manufacturing Modelling

#### Professor Nilay Shah



Professor Nilay Shah is Head of the Department of Chemical Engineering of Imperial College London. Shah implements Quality-by-Design (QbD) approaches to model costing

models and systems analyses of energy as well as vaccine distribution systems. Systems analyses are required for vaccine manufacturing sectors to determine cost efficacy. Market drive is one of the most important determinant factors behind a manufacturing company's decisions towards investigating a vaccine class for a target disease for a particular region(s). Often, barriers to cost effective measures can dissuade companies from pursuing some vaccines.

Shah collaborates across the FVMR Hub by performing comparative QbD studies of established vaccine manufacturing practices as well as assessing innovative or emerging platforms, such as GMMA or RNA. QbD was introduced by the FDA in 2004 as the method that allows the development of manufacturing processes that consider product quality as integral part of the process design. 61 Shah has recently published a review with Shattock and Kontoravdi that compares 4 emergent vaccine approaches: RNA, GMMA, yeast and baculovirus. 62 This systematic approach concluded these emergent technologies in increasing feasibility and decreasing risk in the order of yeast platform, ADDomer platform, followed by RNA and GMMA platforms.

"Shah collaborates across
the FVMR Hub by performing
comparative QbD studies
of established vaccine
manufacturing practices as
well as assessing innovative or
emerging platforms, such as
GMMA or RNA."

#### Dr Cleo Kontoravdi



Dr Cleo Kontoravdi is currently Reader in Biosystems Engineering in the Department of Chemical Engineering at Imperial College London. Kontoravdi has expertise in systems engineering and its

application to bioprocessing. Kontoravdi's team uses model-based tools and is closely collaborating with Professor Shah and Dr Polizzi within the Hub, to model established technologies from industrial partners as well creating robust models for more emerging vaccine technologies.

Kontoravdi has closely collaborated with GSK towards modelling the manufacturing process of GMMA to support its enhancement towards becoming a more feasible vaccine across multiple disease targets. Current focus is optimising the use of GMMA against *Shigella sonnei* and non-typhoidal *Salmonella*. Kontoravdi's analyses will support the progress of GMMA technologies within GSK, which may impact populations in LMICs; whilst her Quality-by-Process analyses are being applied to vaccines being investigated across the Hub.

"Kontoravdi has expertise in systems engineering and its application to bioprocessing."

# **Translational** Research



### National Institute for Biological Standards and Control

The National Institute for Biological Standards and Control (NIBSC) supports the assurance of quality testing for biological medicines, vaccines and therapeutics within the UK and with numerous international partners. NIBSC supplies over 90% biological standards to the WHO - NIBSC is the leading WHO Collaborating Centre and International Laboratory for Biological Standards, Essential Regulatory Laboratory for Influenza, the WHO Collaborating Centre for Reference & Research on Poliomyelitis and the WHO Global Specialised Polio Network Laboratory, NIBSC is also the UK's Official Medicines Control Laboratory. NIBSC comprises expert teams on virology, bacteriology and biotherapeutics. Their Division of Virology is divided into 4 main groups: influenza, polio, live vaccines and inactivated vaccines. They perform quality control tests, such as batch release assays, for a range of vaccines, in partnership with international

"Within the FVMR Hub, NIBSC supports the adherence to regulatory and translational aspects of vaccine research and candidates active within the Hub."

vaccine manufacturers. They furthermore conduct underpinning research resulting in publications in journals such as Vaccine, Frontiers in Immunology and Nature Communications.

Within the FVMR Hub, NIBSC supports the adherence to regulatory and translational aspects of vaccine research and candidates active within the Hub. NIBSC has been in close contact regarding GMMA, RNA and yeast-based vaccines researched by the Hub, particularly for assay development for vaccine potency measurements. NIBSC is also collaborating with DCVMN towards establishing a training programme for DCVMN members to train on-site at NIBSC on preferred quality control assay training.



#### NHS Blood and Transplant

The Molecular Therapies at The Clinical Biotechnology Centre (CBC) within the NHS Blood and Transplant develop quality assured nucleic acid- and protein-based therapeutics for healthcare, which includes GMP production of biologics, such as RNA. CBC performs quality control services for investigational medicinal products within the UK as well as advices on regulatory issues. CBC received the 'Best Clinical Biotechnology Research Facility – UK' award in 2017 by International Life Sciences Awards.

In close collaboration with Professor Robin Shattock, CBC is developing protocols for the GMP production of RNA, improving on capping and purifying strategies, along with a custommade, single-use manufacturing setup to allow engineering batches. RNA represents one of the earliest phases of vaccine candidates of interest within the Hub, and CBC's parallel support in optimising synthetic protocols will streamline the translation and transfer of technology to LMIC partners, nominally the UVRI in Uganda.



#### Centre for Process Innovation

The Centre for Process Innovation (CPI) supports UK research partners by offering process development and manufacturing solutions for biologics. Their state-of-the-art facilities include microbial, mammalian and viral cell culture capabilities to pilot scale. Their focus is on rapid process development, analytical characterisation, formulation, scale-up and GMP-ready manufacturing. CPI operates an ISO 9001:2015 Quality Management System but do not manufacture material for clinical trial. CPI utilises high throughput automated systems for upstream and downstream development and includes the 24 bioreactor ambr® 250 system amenable for mammalian or microbial processes that allows systematic investigation towards optimising culture or fermentation parameters.

The FVMR Hub has partnered with Innovate UK's KTN to launch a call for UK manufacturers and researchers to access CPI's expertise and labs towards goals that align with the Hub. Professor Nicola Stonehouse from the University of Leeds in the UK is partnering with CPI towards the upscaled manufacturing of yeast-based vaccine candidates for polio. The FVMR Hub continues to support UK-based researchers and manufacturers of vaccine ingredients that can impact populations within LMICs.

### **Patents**

The Future Vaccine Manufacturing Research Hub is committed to ensuring research performed by Hub members includes translational goals, such as our research of emergent vaccine candidates by Incepta (Bangladesh) and Vabiotech (Vietnam) as well as established technologies by GSK (Italy) and Aimei Hissen Vaccine (Dalian) Co., Ltd. (China).

As of June 2019, the FVMR Hub has output 5 filed patents:

- 1 Makatsoris, C, UK Patent Application No. 1906422.9, Microfluidic Sensing and Control System
- Makatsoris, C, UK Patent Application No. 1906421.1, Microfluidic Filtration Apparatus
- Makatsoris, C,UK Patent Application No. 1906413.8, Microfluidic Processing Apparatus and Method.
- 4 Liem Bui-le, Alex Brogan, Jason Hallett. Stabilisation of therapeutic proteins (1908914.3).
- Robin Shattock, Anna Blakney, Paul McKay. Stealthicons: RNA replicons with cis-encoded viral protein interferon inhibitors (1908729.5).

"Next to clean water, vaccines have the greatest impact on human health. Our mission is to facilitate the manufacture of life saving vaccines."

# **Training**

Imperial College London's Future Vaccine
Manufacturing Hub takes pride in the successful
training that is being offered, to students,
more experienced researchers, as well as
manufacturing staff from LMICs.

Paul Kitandwe, a PhD student being trained in a secondment within Professor Robin Shattock's labs in the Department of Medicine at Imperial College London, is performing research that supports the goals of the FVMR Hub. From Uganda, Paul Kitandwe has been a guest student in the Shattock labs since June 2019 and is studying RNA vaccines targeting Rift Valley Fever and aims to collaborate with CBC (NHSBT) when the project is more developed and the protocols are established and optimised at the lab scale.

Mac Trong, a staff member from the company Vabiotech in Vietnam, seconded in the labs of Professor Imre Berger at the University of Bristol. The Berger labs are partnering with Vabiotech within the FVMR Hub towards transferring and establishing baculovirus-based vaccine manufacturing protocols for influenza targets. Such innovative technologies are aiming to transform the repertoire of products available from Vabiotech.

Professor Xiao-ning Xu from Imperial College London is hosting and training staff from Aimei Hissen Vaccine (Dalian) Co., Ltd. in China. Since March 2019, Ms Jiaping Yu is seconding within the Xu labs, whilst Ms Kun Xu is planning to second from July 2019. This collaboration aims to exploit yeast manufacturing platforms towards the production of multiple vaccine candidates against EV71 as well as chikungunya.

Top image: Paul Kitandwe, a staff member of UVRI in Uganda, training within Professor Robin Shattock's labs at Imperial College London in 2019.



# **Training**

Dr Karen Polizzi is training 2 researchers from Incepta Ltd (Bangladesh). Polizzi is an expert in yeast and is researching super-strains as well as improved methods of fermenting yeast to express VLPs against HPV and Hepatitis E. Incepta Ltd is planning to support transfer of this technology by subsequently collaborating with FVMR Hub partner NIBSC in 2020.

Professor Harris Makatsoris has gradated one MSc in distributed vaccine manufacturing and one group of 7 students under the theme "Reconfigurable micro-factories for Future Vaccines Manufacturing", whilst two MSc theses are currently ongoing.

The FVMR Hub proudly trains more experienced researchers, such as postdoctoral researchers, in their career developing and progression. Yunqing (Frank) Zhu, a postdoctoral researcher in the Stevens labs within the FVMR Hub, has recently been appointed Professor at Tongji University in Shanghai. Alex Brogan, a postdoctoral researcher in the Hallett labs within the FVMR Hub, has very recently been appointed as Lecturer at King's College London.

Dr Zoltan Kis has been active in training activities, such as by attending:

- Course on bioprocess modelling, simulation, optimization & production scheduling, using SuperPro Designer and SchedulePro, organised by Intelligen, Inc. at TU Berlin, Germany, 23-24 October 2018.
- BBSRC Strategic Training Awards for Research Skills (STARS) School, with GMP site visits to Fujifilm Diosynth Biotechnologies and to GSK Barnard Castle, hosted at the Centre for Process Innovation, Darlington, UK, 9-14 September 2018.
- BioProNET Bioprocess Intensification Symposium, University College London, UK, 4 July 2018.
- Biochemical Engineering Pilot Plant
   Experience: Cell-free protein synthesis, Future
   Targeted Healthcare Manufacturing Hub,
   University College London, 19-22 June 2018.
- BioProNET workshop on Applications of Genome Editing in Biomanufacturing, Cambridge Science Park, 18 June 2018.

Dr Rochelle Aw presented FVMR Hub research at the RPP10 conference in Crete, Greece. 63

## **Publications**

Charles Vragniau, Joshua C. Bufton, Frédéric Garzoni, Emilie Stermann, Fruzsina Rabi, Céline Terrat, Mélanie Guidetti, Véronique Josserand, Matt Williams, Christopher J. Woods, Gerardo Viedma, Phil Bates, Bernard Verrier, Laurence Chaperot, Christiane Schaffitzel, Imre Berger, and Pascal Fender. "Synthetic self-assembling ADDomer platform for highly efficient vaccina-tion by genetically encoded multiepitope display." Science Advances. 2019. 5: eaaw2853.

Ankur Matreja and Gordon Dougan. "Molecular epidemiology and intercontinental spread of cholera." *Vaccine*. 2019.

Anna K. Blakney, Paul F. McKay, Bárbara Ibarzo Yus, Yoann Aldon, and Robin Shattock. "Inside out: optimization of lipid nanoparticle formulations for exterior complexation and in vivo delivery of saRNA." *Gene Therapy*. 2019.

Zoltán Kis, Maria M. Papthanasiou, Raul Calvo-Serrano, Cleo Kontoravdi, and Nilay Shah. "A model-based quantification of the impact of new manufacturing technologies on developing country vaccine supply chain performance: a Kenyan case study." Journal of Advanced Manufacturing and Processing. 2019

Maria M. Papthanasiou, Baris Burnak, Justin Katz, Nilay Shah, Efstratios N. Pistikopoulos. "Assisting continuous biomanufacturing through advanced control in downstream purification." Computers & Chemical Engineering. 2019. 125: 232-248.

Anna K. Blakney, Paul F. McKay, Bárbara Ibarzo Yus, Judith E. Hunter, Elizabeth A. Dex, and Robin J. Shattock. "The Skin You Are In: Design-of-Experiments Optimization of Lipid Nanoparticle Self-Amplifying RNA Formulations in Human Skin Explants." ACS Nano. 2019. 13(5): 5920-5930.

Anna K. Blakney was awarded a Provost's Award for excellence in animal research for the above work.

Anna K. Blakney, Gokhan Yilmaz, Paul F. McKay, C. Remzi Becer, Robin J. Shattock. "One Size Does Not Fit All: The Effect of Chain Length and Charge Density of Poly(ethylene imine) Based Copolymers on Delivery of pDNA, mRNA, and RepRNA Polyplexes." Biomacromolecules. 2018. 19(7): 2870-2879.

Anna K. Blakney, Paul F. McKay, Robin J. Shattock. "Structural Components for Amplification of Positive and Negative Strand VEEV Splitzicons." *Frontiers in Molecular Biosciences*. 2018. 5: 71.

Luke Muir, Paul F. McKay, Velislava N. Petrova, Oleksiy V. Klymenko, Sven Kratochvil, Christopher L. Pinder, Paul Kellam, Robin J. Shattock. "Optimisation of ex vivo memory B cell expansion/differentiation for interrogation of rare peripheral memory B cell subset responses." Wellcome Open Research. 2018. 2: 97.

Zoltán Kis, Robin Shattock, Nilay Shah, Cleo Kontoravdi. "Emerging Technologies for Low-Cost, Rapid Vaccine Manufacture." *Biotechnology Journal*. 2019. 14: 1800376.

# Awards and Honours

Congratulations to Anna K. Blakney,
who was awarded a Provost's Award for
excellence in animal research<sup>64</sup> for her
experiments reported in "Anna K. Blakney,
Paul F. McKay, Bárbara Ibarzo Yus, Judith E.
Hunter, Elizabeth A. Dex, and Robin J. Shattock.
"The Skin You Are In: Design-of-Experiments
Optimization of Lipid Nanoparticle SelfAmplifying RNA Formulations in Human Skin
Explants." ACS Nano. 2019. 13(5): 5920-5930".



Congratulations to Alex Brogan, who was awarded the Postdoc and Fellows
Development Centre (PFDC) Reps Award
2018.65 (pictured below)



Congratulations to Yunqing (Frank) Zhu, previously a postdoctoral researcher within the FVMR Hub, for being appointed as Professor at Tongji University in Shanghai.



Congratulations to *Alex Brogan*, previously a postdoctoral researcher within the FVMR Hub, for being *appointed as Lecturer* at King's College London.

Congratulations to Professor Nilay Shah, who received the Sargent Medal<sup>66</sup> from the Institution of Chemical Engineers for his "world-leading work in the field of process systems engineering, in particular, in the development and application of mathematical models to analyse, design and optimise complex process and energy systems".



### Outreach



FVMR Hub members Anna Blakney and Karnyart Samnuan participated the European Research & Innovation days 'Science is Wonderful!' event in Brussels, which consisted of educating 1,500 children over two days about vaccines.



The FVMR Hubs research was prominently displayed at the 2019 World Economic Forum in Davos, Switzerland, with talks delivered by Profs Robin Shattock and Jason Hallett, which was highlighted by Imperial College London's News website<sup>67</sup> as well as WatsUp Africa.<sup>68</sup>



In Jan 2019, Professor Robin Shattock was interviewed by the BBC World News on the use of vaccines against "Disease X".

Professor Robin Shattock said, "We believe that synthetic self-amplifying RNA based vaccines offer the best opportunity for a 'just in time' response to infectious outbreaks, providing the needed technological shift to aggressively redefine the timelines for vaccine production."

Professor Harris Makatsoris has published two blogs on the need for Pop-Up Vaccine Factories, referencing the FVMR Hub, in Geographical<sup>69</sup> and the Huffington Post<sup>70</sup>.

Professor Harris Makatsoris presented at the DCVMN Supply Chain Working Group in June 2019.

Highlights from the Future Vaccine
Manufacturing Research Hub are highlighted in
the twitter account @vaxresearch.

35% of the PIs for the academic and developing world vaccine manufacturing partners within the FVMR Hub are female.

The website for the FVMR Hub has been updated in 2019 and includes reliable information on vaccines, as well as suggested reading, presented in lay language for the general public.

### **Endnotes**

- 1 https://www.who.int/bulletin/volumes/90/3/ 11-093427/en/
- 2 https://apps.who.int/iris/bitstream/ handle/10665/258763/WER9234.pdf;jsessionid= A69976E64D17D9CB7664112536DF4018? sequence=1
- 3 https://www.who.int/cholera/publications/ global-roadmap-summary.pdf?ua=1
- 4 https://www.hillemanlabs.org/
- 5 www.euro.who.int/en/health-topics/ communicable-diseases/influenza/vaccination/ influenza-vaccination-coverage-and-effectiveness
- 6 https://www.nature.com/articles/ d41586-018-05889-1
- 7 https://apps.who.int/iris/bitstream/hand le/10665/311184/9789241515320-eng.pdf?ua=1
- 8 https://www.thelancet.com/action/showPdf? pii=S1473-3099%2818%2930364-5
- 9 https://academic.oup.com/jid/article/219/ Supplement\_1/S14/5304929
- 10 http://www.vabiotech.com.vn/?lang=en
- 11 https://www.ncbi.nlm.nih.gov/pmc/articles/ PMC6466381/pdf/viruses-11-00198.pdf
- 12 https://www.frontiersin.org/articles/10.3389/fpubh.2019.00056/full
- 13 https://www.who.int/immunization/research/ forums\_and\_initiatives/1\_Wlliam\_Ampofo\_ Vaccine\_Manufacturing\_Africa.pdf?ua=1
- 14 http://www.pasteur.sn/
- 15 http://egyvac.vacsera.com/egyvacProfile.pdf
- 16 https://www.biovac.co.za/
- 17 http://www.pasteur.tn/
- 18 https://www.sciencedirect.com/science/article/ pii/S1877282X13000039
- 19 https://www.who.int/medicines/ethiopia\_ pharmaceutical\_manufacturing/en/
- 20 https://www.ncbi.nlm.nih.gov/pmc/articles/ PMC4203350/pdf/emmmooo6-0708.pdf
- 21 https://iris.wpro.who.int/bitstream/handle/ 10665.1/14191/HFMD-20180828.pdf
- 22 https://www.nature.com/articles/ \$41598-019-41285-z

- 23 https://www.nejm.org/doi/10.1056/NEJMoa1303224 ?url\_ver=Z39.88-2003&rfrid=ori%3Arid%3Acrossref .org&rfr\_dat=cr\_pub%3Dwww.ncbi.nlm.nih.gov
- 24 http://jphe.amegroups.com/article/view/3677/4439
- 25 https://www.tandfonline.com/doi/full/10.1586/ 14760584.2016.1138862
- 26 https://www.nejm.org/doi/10.1056/NEJMoa1303224 ?url\_ver=Z39.88-2003&rfr\_id=ori:rid:crossref. org&rfr\_dat=cr\_pub%3dwww.ncbi.nlm.nih.gov
- 27 https://st3.ning.com/topology/rest/1.o/file/get/2748681047?profile=original
- 28 https://www.who.int/immunization/diseases/hpv/en/
- 29 https://www.who.int/denguecontrol/arbo-viral/ other\_arboviral\_chikungunya/en/
- 30 https://www.gsk.com/en-gb/behind-the-science/ innovation/welcome-to-the-golden-age-ofvaccine-innovation/
- 31 https://onlinelibrary.wiley.com/doi/pdf/10.1002/biot.201800376
- 32 https://stm.sciencemag.org/content/11/497/eaaw2888
- 33 https://www.pnas.org/content/115/41/10428
- 34 https://www.who.int/news-room/fact-sheets/ detail/salmonella-(non-typhoidal)
- 35 https://www.bbc.co.uk/news/health-48512923
- 36 https://spiral.imperial.ac.uk:8443/handle/ 10044/1/31339
- 37 https://www.frontiersin.org/articles/10.3389/fimmu.2017.00149/full
- 38 https://linkinghub.elsevier.com/retrieve/pii/ So264-410X(10)01786-X
- 39 https://www.sciencedirect.com/science/article/ pii/So264410X1001786X?via%3Dihub
- 40 https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0152038
- 41 http://europepmc.org/backend/ptpmcrender.fcgi? accid=PMC2662964&blobtype=pdf
- 42 https://www.nature.com/articles/nature10392
- 43 https://www.ncbi.nlm.nih.gov/pmc/articles/ PMC3491877/
- 44 https://www.nature.com/articles/s41598-017-16172-0

- 45 http://www.imperial.ac.uk/department-of-medicine/ research/infectious-diseases/virology/immunology/ centre-for-immunology-and-vaccinology/
- 46 https://www.sciencedirect.com/science/article/pii/ S1074761301002552?via%3Dihub
- 47 https://pubs.acs.org/doi/pdf/10.1021/jacs.5b13425
- 48 https://www.nature.com/articles/s41557-018-0088-6
- 49 http://www.nature.com/nmat/journal/v12/n6/full/ nmat3627.html
- 50 https://www.nature.com/articles/nmat4249
- 51 https://www.nature.com/articles/s41467-018-06397-6
- 52 http://www.sciencemag.org/content/346/6205/ 1247390.abstract?sid=99af58a4-9595-4821-8ade-777e763d2b8c
- 53 https://www.nature.com/articles/s41586-019-0956-2
- 54 https://www.nature.com/articles/ncomms15509
- 55 https://www.nature.com/articles/nmat3949
- 56 https://www.nature.com/articles/nchem.1793
- 57 https://www.tandfonline.com/doi/full/10.1080/ 09537287.2018.1540057
- 58 https://linkinghub.elsevier.com/retrieve/pii/ S0142-9612(08)01020-X
- 59 https://www.ncbi.nlm.nih.gov/pmc/articles/ PMC6180194/
- 60 https://pubs.acs.org/doi/10.1021/acsami.6bo5041
- 61 https://www.sciencedirect.com/science/article/pii/Soo98135418307464?via%3Dihub
- 62 https://onlinelibrary.wiley.com/doi/full/ 10.1002/biot.201800376
- 63 http://efbiotechnology.org/RPP/C223
- 64 https://www.imperial.ac.uk/research-and-innovation/ about-imperial-research/research-integrity/animalresearch/awards/2017-winners/
- 65 https://www.imperial.ac.uk/news/187038/chemicalengineer-receives-postdoc-fellows-development/
- 66 http://www.imperial.ac.uk/news/190208/imperialstaff-recognised-outstanding-contributions-chemical/ ?platform=hootsuite
- 67 https://www.imperial.ac.uk/news/189957/imperialscientists-present-vaccine-revolution-world/?utm\_ term=global+leaders+at+the+World+Economic+Forum &hootPostID=29458e7164ob25fd58507122bfecd5a5

- 68 http://development.watsupafrica.com/news/ distributed-production-of-rna-vaccines-for-agileresponse-to-outbreaks-robin-shattock/
- 69 https://geographical.co.uk/opinion/item/2756pop-up-vaccine-factories
- 70 https://www.huffingtonpost.co.uk/entry/why-theworld-needs-pop-up-vaccine-factories\_uk\_ 5af29fa5e4bo13a9682bfbca







This research is funded by the Department of Health and Social Care using UK Aid funding and is managed by the Engineering and Physical Sciences Research Council (EPSRC, grant number: EP/Ro13764/1). The views expressed in this publication are those of the author(s) and not necessarily those of the Department of Health and Social Care.

Future Vaccine Manufacturing Research Hub Imperial College London Department of Medicine St Mary's Campus Norfolk Place London W2 1PG

**Contact us:** Please contact us using the <u>Online Contact Form here</u> found at our website below.

imperial.ac.uk/future-vaccine-hub