Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Microbes and Infection 21 (2019) 125–128

Contents lists available at ScienceDirect

Microbes and Infection

journal homepage: www.elsevier.com/locate/micinf

Highlight

Guns N′ viruses☆

Keywords:
Ebola virus
Democratic Republic of Congo 2018 outbreak

At the time of me writing this sentence, about 354 people have died of Ebola in the province North Kivu of the Democratic Republic of Congo (DRC). At the time of you reading it, this number will have most certainly increased, given that the disease just spread to Butembo, a major city of nearly a million inhabitants and a key trading and transit center to the rest of the country and the neighboring Uganda.[1] Just one week after the official end of the Équateur province outbreak with 54 cases and 33 deaths, the Kivu Ebola outbreak started on the 1st of August 2018 and has since then acquired the infamous title of the second-largest and -deadliest Ebola outbreak in history, runner-up to the 2014 outbreak in West Africa. A history of over 40 years nonetheless, as the virus was identified in 1976 and has struck tropical sub-Saharan Africa countless times. The DRC alone is at its 10th outbreak, yet it wasn't until the 2013–2016 outbreak with 28 652 infected and 11 652 killed people that we started finally worrying about the possibility that globalization and climate change might transform a local problem into a pandemic. Completely caught off-guard by the extent of the 2014 epidemic, the efforts to avoid a replay have nevertheless been manifold since, covering all stages from prevention to diagnosis and treatment.

Prevention rhymes with vaccination, as is shown by the highlighted paper from Dan Li and colleagues from China and France. Unlike most studies, which focus on Ebola virus (EBOV) glycoprotein, the authors screened the EBOV nucleoprotein for cytotoxic T-lymphocyte (CTL) epitopes and demonstrated that five candidates elicit effective CTL responses in mice [1]. Hopefully, the translation to humans won't be required though, as the study focuses exclusively on epitopes binding the HLA-A11 allele, whose frequency is over 50% in the Chinese but only 1% in the African population, where the virus is usually wrecking havoc. To date, about eight other vaccines aimed at a broader public are at various stages of clinical trials. One of them is currently in use and licensed by Merck: the rVSV-ZEBOV is a recombinant, replication-competent vaccine consisting of the vesicular stomatitis virus (VSV) expressing the Zaire EBOV glycoprotein vaccine and was already developed, and its protection against Ebola and Marburg viruses in nonhuman primates proven and published in 2005 [2], but due to a "lack of market", it spent the next decade sitting on a shelf.[2] Only 5000 deaths later during the West Africa outbreak in 2014, it got hastily dusted and rushed through the essential safety tests in humans. A ring vaccination trial conducted in Guinea and Sierra Leone in 2015–16 on nearly 12 000 individuals certified it to be up to 100% efficient [3,4]. As a regulatory authority has not yet officially approved the vaccine, it is to date used in the DRC under the *compassionate use trial* protocol and has significantly contributed to quenching the Équateur province outbreak.

On the treatment front, which is still lacking any fully convincing counter-measure to fight the virus, a group of American researchers very recently found potential help from within the human cell itself. Given that viruses rely heavily on the host molecular machineries for every single step of their life cycle, Jyoti Batra and colleagues proceeded to map in detail the entire EBOV-host protein–protein interactome *via* affinity tag-purification mass spectrometry (AP-MS). Out of 194 interactions they found, one of the strongest takes place between the viral transcription regulator VP30 and the host ubiquitin ligase RBBP6 that mimics the binding of VP30 to the viral nuclear protein NP. The equilibrium between viral mRNA synthesis and genome RNA replication is regulated by the phosphorylation status of VP30: NP recruits the protein phosphatase 1 or 2A, leading to the dephosphorylation of VP30 and promoting its transcriptional activity. Consequentially, knock-down of RBBP6 stimulated viral transcription and elevated EBOV replication, while overexpression of the protein or even just a short peptide containing the RBBP6-VP30 binding motif potently inhibited both. Ideally, these findings could give raise to the production of small molecule drugs that would disrupt the viral life cycle [5].

However, the outcome of any treatment relies essentially on an early and accurate diagnosis of the disease. Yet, regions with frequent hemorrhagic fever outbreaks like Ebola tend to coincide with low-resource regions beleaguered by a flock of other endemic diseases with similar early symptoms, such as malaria or Lassa fever. So far, mainly RT-PCR had been used for definitive diagnosis of Ebola, but the technique requires trained personnel and a minimum of laboratory infrastructure. A team of researchers from the States, Senegal and Guinea decided to tackle the urgent need for fast portable diagnostics

☆ Article highlight based on "Identification of novel HLA-A11-restricted T-cell epitopes in the Ebola virus nucleoprotein" by Dan Li et al. [1].

[1] https://www.yahoo.com/gma/2nd-deadliest-ebola-outbreak-history-spreads-major-city-191404844–abc-news-topstories.html?guccounter=1.

[2] https://www.nytimes.com/2014/10/24/health/without-lucrative-market-potential-ebola-vaccine-was-shelved-for-years.html?_r=0.

https://doi.org/10.1016/j.micinf.2019.01.001

made of ambient temperature-stable reagents that can be used in low-infrastructure settings. They just published a immunoassay technology based on surface-enhanced Raman scattering (SERS) that simultaneously detects antigens from Ebola, malaria and Lassa fever in 30 min from a single blood sample without the requirement for trained personnel, laboratory infrastructure or even electricity [6]. The core elements of the system are "Raman reporter" molecules - different reporters produce unique signatures of light wavelengths after a specific incident wavelength is scattered by them. In brief, gold particles are first coated with a layer of one Raman reporter then encapsulated in a silica shell spiked with antibodies either for Ebola, Lassa or malaria. Each type of antibody corresponds to a certain type of reporter molecule, constituting a *SERS nanotag*. More antibodies are conjugated to magnetic microparticles in a way that a certain antigen can be sandwiched between the antigen bound to a nanotag and the one complexed to the magnetic particle. For diagnosis, a blood sample is mixed with dried nanotags and magnetic microparticles in a vial. Subsequently, a magnet pulls the microparticles and the SERS nanotag–antigen–microparticle complexes to the side of the wall of the reaction vessel, a 785-nm laser is shone at the pellet and the scatter spectrum recorded. The SERS signal directly translates antigen identity into a distinctive spectrum and is interpreted automatically. Upon testing on clinical samples, the system displayed 90% sensitivity and 97,9% specificity for Ebola detection respectively. Limited blood handling increases the biosafety of the technology, the SERS nanotags are stable at ambient temperature and in biological fluids, no sample preparation or wash steps are needed and the entire device is easily transportable and infrastructure independent - quite the list of plus points, except for some doubts concerning the affordability of a gadget containing an internal computer, a Raman spectrometer, a laser and gold beads …

Mind you, the prize of the nifty box is not even the main obstacle separating the greatest progress in prevention, diagnosis and treatment from bitter reality. As a rule of thumb, the more a nation emphasizes attributes like, "democratic" or "people's" in their title, the less of the latter is usually found *in situ*. Thereby, more than the lethal virus, the local population of the latest hot spots of Ebola outbreaks in eastern Congo fears the so-called Mai–Mai, about a hundred militia groups in constant fight with government forces. Chronic violence fueled by an independence war, the genocide in neighboring Rwanda and the increasing demand for rare earth minerals, alias "conflict minerals", used as much for our everyday electronic devices as to finance the local militia have probably killed millions over the past 50 years - quite a different order of magnitude from the EBOV achievements. Villages are regularly raided by armed groups or marauding government forces, which extort illegal taxes, rape and kill civilians. As a consequence, the latter are suspicious and fearful of any outsiders, health workers included. Once these have finally negotiated their safe passage with the militia leaders (with moderate success, as several treatment sites have been ravaged by armed groups), they have to face the rejection by the locals, which can very well mean being charged by a machete-wielding grandmother refusing that they take an infected infant from the family.[3]

In addition, the upcoming national elections on December 30th, meant to replace the outgoing President Joseph Kabila, in power since 2001, are throwing oil by the gallon on the fire of unrest in the country, with politicians unscrupulously exploiting the Ebola crisis. Rumors were spread that the government or foreigners deliberately disseminated the virus and that thermo-guns are weapons to steal votes. The decision by the electoral commission (CENI) to cancel voting in the cities of Beni, Butembo and their surroundings because of the Ebola crisis and militia violence was the final straw: protesters attacked the CENI office as well as the headquarters of the government agency in charge of coordinating the Ebola response in Beni and an Ebola isolation center, sending patients fleeing.[4]

Last October, the Nobel Price of Peace 2018 went to Nadia Murad and Denis Mukwege. What unites them is the everlasting use of sexual violence as a weapon of war. Nadia Murad, a member of the Yazidi minority in northern Iraq, was abducted by members of the Islamic State (IS) and held as a sex slave. Denis Mukwege is "The Man Who Mends Women",[5] a physician who has dedicated his life to helping the victims of sexual violence due to the interminable civil war in the DRC. In its official declaration, the Norwegian Nobel committee quotes Mukwege's basic principle that "justice is everyone's business".[6] Acknowledging the subject *via* the prestigious award is a decent start, but the current situation in eastern DRC is a disastrous buildup of human tragedy.

Perhaps, deadly viruses, the origin of our cell phone's innards and the abuse of the female body as a battlefield should be everyone's business too.

1. Biosketch of Dr.Sun and Dr.Zhou's research team

Research of our team focuses on the development of transgenic humanized MHC mouse model, pathogenesis of emerging infectious diseases, and development of vaccines against highly pathogenic microbes such as SARS-CoV,MERS-CoV, Influenza viruses and Ebola virus.

Dr.Shihui Sun (left) is an Associate Professor. She obtained her PhD on genetics, especially the transgenic animal models, at Beijing Institute of Biotechnology in 2005. Currently, her research focuses on the establishment of specific animal models, such as HLA-A11/DR1 for the pathogenesis and vaccination studies about highly pathogenic pathogens including MERS-CoV, Ebola and H5N1 influenza virus.

Dr.Lin Zeng (second right) is a Professor of Laboratory Animal Center of the Academy of Military Medical Science , Beijing, China. His research focuses on laboratory animal science, including developement of new animal strains and animal models for the studies of human diseases. He has systemically studied the mechanism of hairless phenotype in Uncv mice.

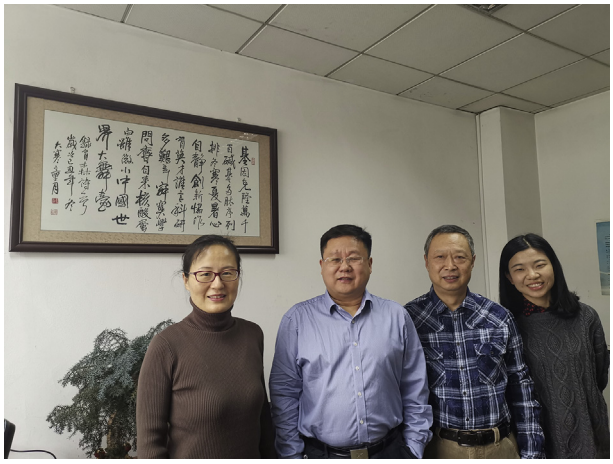
Yusen Zhou (second left) is a Professor of Microbiology and Immunology, and Head of Department of Infection and Immunity, State Key Laboratory of Pathogen and Biosecurity at the Beijing Institute of Microbiology and Epidemiology, China. His research covers emerging highly pathogenic infectious diseases caused by coronaviruses and other infectious viruses, as well as the development of vaccines and animal models of these infectious diseases.

[3] https://www.nytimes.com/2018/12/26/world/africa/ebola-congo.html?action=click&module=Top%20Stories&pgtype=Homepage.

[4] https://www.telegraph.co.uk/news/2018/12/27/congo-protesters-ransack-ebola-isolation-centre-amid-widespread/.

[5] *The Man Who Mends Women: The Wrath of Hippocrates* is a 2015 Belgian documentary by Thierry Michel and Colette Braeckman about Denis Mukwege.

[6] https://www.nobelprize.org/prizes/peace/2018/press-release/.



2. Interview with Dr.Shihui Sun

2.1. What was your motivation to search for Ebola virus nucleoprotein epitopes that bind specifically to HLA-A11?

Ebola is a major threat to human health. The role of immune response induced by Ebola virus infection in viral pathogenesis and immune protection needs to be further studied. Humoral immune responses, especially neutralizing antibodies, induced by viral infection have protective effects. However, the role of cellular immune response induced by Ebola virus infection is not systematically studied. Starting with the screening and identification of immune restrictive-epitopes, we are using our humanized MHC transgenic mice (HLA-A11/DR01,HLA-A2/DR15 and HLA-A2/DP4) to determined the immune restrictive-epitopes for different ethnic groups, and to explored the role of major viral protein epitopes in immune protection.

2.2. What was your first reaction when you faced the results? Did you expect them?

It was very delight for us to find out five epitopes which can induce effective CTL responses. Because the screening was base on the humanized HLA-A11/DR1 transgenic mouse model, the candidate epitopes will be used to explore the role of major viral protein epitopes in immune protection.

2.3. How will the project go on?

We will continue to identify and map CTL and Th epitopes of major proteins of Ebola virus, providing basic data for the development of more effective vaccines.

2.4. What is the take-home message of the article?

Development of vaccines is a long-term process and screening of effective epitopes is very important for the development of an effective vaccine. The candidate epitopes we identified here will be very useful for designing and developing novel vaccines.

2.5. Do you have a personal motto, quote or leading sentence?

Life sometimes is not to do what you like, but to like what you do.

2.6. What advice would you give to the young next-generation scientists?

Strive for dream with passion and innovation. Never give up!

2.7. What is your favourite hang-out method after a tough day at the lab?

Going to gym.

2.8. In your opinion, what are the three most important (scientific) discoveries of the last decade?

CRISP/Cas9 gene editing, Chimeric antigen receptor T-cell immunotherapy and RNA interference.

2.9. If you could travel back in time – what historical personality would you like to meet and what scientific discovery to assist to?

I would like to meet Watson and Crick. It was their discovery of DNA double helix structure that opened the era of molecular biology and the exploration of mystery of life.

2.10. If you could travel forth in time – what eventual invention would you like to check out?

I would like to see effective universal vaccines against highly pathogenic microbes to be used in humans.

3. Background

- Ebola virus (EBOV) is an enveloped negative-sense RNA filovirus
- EBOV is a zoonotic pathogen hosted probably by fruit bats
- It causes severe and often lethal hemorrhagic fever in humans with a mortality rate up to 90%
- Human-to-human transmission happens mainly through body fluids
- The largest outbreak took place in West Africa between 2013 and 2016 and caused 11 652 deaths

4. In a nutshell

- The nucleoprotein of the Ebola-Makona strain and a GFP reporter were cloned into a recombinant adenovirus vector (Ad5-EBOV-NP)
- HLA-A11/DR1 double transgenic mice produced a robust and specific IgG antibody after Ad5-EBOV-NP vaccination
- Potential HLA-A11-restricted epitopes in the EBOV-NP protein were predicted *in silico* and 10 candidate peptides were tested on primed splenocytes from Ad5-EBOV-NP immunized mice

5. candidates elicited significant IFN-γ production specific to cells from HLA-A11/DR1 transgenic mice

Conflict of interest

There is no conflict of interest.

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Sophia Häfner
University of Copenhagen, BRIC Biotech Research & Innovation Centre, Lund Group, 2200 Copenhagen, Denmark
E-mail address: sophia.hafner@bric.ku.dk.

29 December 2018
Available online 23 January 2019