# Editorial

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**Biographical notes:** Aldar S. Bourinbaiar is the CEO of Immunitor USA Inc., in charge scientific and business aspects of the company. Currently, he works on development of oral vaccines against a variety of viral infections. He has published over 100 papers on *molecular biology, oncology*, immunology and virology to his credit.

## 1 Introduction

This issue is dedicated primarily to vaccines in their multiple forms and functions with contributors from many countries. It has not been an easy task to gather and accommodate such a diversity of ongoing research. Clearly, there is no lack of ideas or approaches undertaken by investigators in Armenia, China, Denmark, Finland, India, Mexico, Nigeria, Russia, South Africa, Switzerland, Taiwan, Thailand, Ukraine and USA. I am proud to present their work in this special, truly international issue, now featured on the pages of *International Journal of Biotechnology*. Below is a brief introduction to each paper, which will appear in alphabetical order according to the name of the first author.

Dr. Jeremiah Abalaka of Medicrest hospital in Nigeria has the honour to lead the list not only because his name starts with 'A' but also because of his work. He is the first person in the world to claim to have developed an effective prophylactic AIDS vaccine. He has so much confidence in it that he had injected himself with HIV-infected blood repeatedly and is not infected. He could have been a hero in the 19th century but in today's world morals have changed. The paper he presents deals with the therapeutic aspect of his vaccine. He treated over 4000 AIDS patients with his THIVAC vaccine, the preliminary results of which he published last year in the journal *VACCINE*. The paper presented here provides additional evidence of the beneficial outcome as supported by statistical analysis of changes in CD4-positive lymphocyte counts – a surrogate marker in HIV disease. Even though his work was praised by reputed vaccine experts he is more often criticised rather than praised in the lay press. I believe the data he presents are very compelling and may help him to find more support for his courageous work.

Blanca E. Del Rio Navarro and her colleagues in Mexico summarise their own as well as other investigators' studies of so-called immunostimulants, which broadly encompasses compounds producing 'non-specific' immunity. However, the distinction between *bona fide* vaccine and an immunostimulant is increasingly blurry, especially when the latter contains specific pathogen antigens to treat or prevent that same pathogen-caused disease. Thus such an immunostimulant will be by definition a vaccine

(see below paper by Meredith and Chiavaroli). However, with the exception of, perhaps, oral cholera vaccine, almost all these preparations are marketed as immunomodulators or dietary supplements. However, this discrepancy in regulatory terminology appears to be semantic rather than scientific. It can be also argued that the main distinction between vaccines and non-vaccines is whether one uses whole organism or purified antigen thereof. However, rabies, poliovirus, influenza, cholera and many other old-fashioned vaccines are based on immunisation with the whole pathogen and not any particular subunit. Perhaps, the truth lies in the eye of the beholder.

The next paper is offered by the team of Dr. Guanmu Dong of The National Institute for the Control of Pharmaceutical and Biological Products, in Beijing, China. Despite his laconic style, his work speaks volumes. He presents succinctly the enormous undertaking, which is the Phase II trial of his bivalent Hantavirus vaccine on 1168 volunteers. Hemorrhagic fever with renal syndrome caused by this virus is a serious public health problem. Vaccine made by Dong et al., sounds simple to make and easy to test, but anyone familiar with vaccine development will appreciate fully the extent of intellectual effort and plain physical labour needed to successfully accomplish this task. Despite this team's present and past achievements they seldom, if ever, have had a chance to publish outside of China. This issue gives them, for the first time, an occasion to have their remarkable work visible to a wider audience.

Ukrainian doctors Chehetiany, Kutsyna and their colleagues, made an approach that has no precedents in the immunotherapeutic history of AIDS. They bet on a premise that the immunopathogenesis of HIV-infection is inherently an autoimmune process and hence one needs to suppress self-destructive immunity against HIV. While such an approach is getting gradually accepted, as evidenced by three papers in this issue, what they have used as a therapeutic modality is highly unconventional. They have administered Ukrainian-made immunomodulator *Immukrain* or Dzherelo and compared its effect to standard 'cocktail' Antiretroviral Therapy (ART). Dzherelo is an alcohol extract of medicinal herbs that has been successfully used in the past for the treatment of a variety of infectious and autoimmune diseases and preliminary open label trials of these authors have indicated potential benefit in AIDS patients. Surprisingly, their bet bore fruit. Dzherelo has shown superior clinical results than ART. What is more encouraging is that Ukrainian cocktail essentially neutralised the toxic effect of ART when two cocktails were used simultaneously. People are usually sceptical of herbal remedies but this one stands out from the crowded field of HIV therapeutics. Future studies will certainly reveal the full potential of Dzherelo.

Synthetic peptides developed for HIV vaccine mimic linear or conformational epitopes presented by the virus, since they are designed as immunogens for induction of humoral or cellular immune response. What can one do with these peptides if no funding is available for testing them as a vaccine? Raymond Hewer and Debra Meyer from the Department of Biochemistry at the University of Johannesburg in South Africa have encountered precisely this problem. As they had little choice they decided instead to use these peptides as antigens for Enzyme-Linked Immunosorbent Assay (ELISA) development. They review the efficacy of envelope-based synthetic peptides as antigens in HIV diagnostic assays, including those originally made as vaccine components. The majority of these synthetic peptides, even if based on the V3-loop of HIV-1, are designed to be homogenous. The heterogeneous peptides they have prepared through novel synthesis appear to be as good as their homogenous counterparts. At least, it seems that their AIDS vaccine can be useful as a diagnostic.

The most severe form of malaria affecting humans, *Plasmodium falciparum*, is estimated to kill 1–3 million people annually, mostly small children and pregnant women in sub-Saharan Africa. However, despite years of intensive efforts around the world, no vaccine is yet available. Drs. Lars Hviid and Thor Theander from the University of Copenhagen in Denmark have studied the human immune response to malaria in Africa for more than two decades. While many scientists think that the main problems with malaria vaccine development are technical and/or financial, others, including the authors, believe that lack of consideration of how naturally acquired immunity to malaria works is an important factor. In their paper they suggest a completely novel vaccination strategy, aiming at a vaccine that can protect against mortality and severe morbidity, but which will allow persistence of low-grade, asymptomatic infection caused by constant exposure to parasite-transmitting mosquitoes. They argue that this approach will ensure periodic boosting of immunity that appears necessary for the long-lasting protection required of vaccines to be deployed in malaria-endemic areas.

This paper of Dr. Mkhitaryan and his colleagues from Armenia does not deal with a vaccine. The subject of their work is iodine-lithium-α-dextrin (ILαD) – a metallo-organic compound which they have investigated in patients with HIV infection. They have demonstrated that ILαD is safe, can reduce levels of HIV in the blood, increase CD4 T lymphocyte counts, improve patients' quality of life with little or no adverse effects. However, the authors attribute the beneficial effect not to the direct antiviral activity of ILαD but rather to its anti-inflammatory action. In this aspect, the study of Armenian scientists supports the notion that the preservation of CD4+ T cells through reduced immune activation rather than the establishment of a lower viral load may be more relevant in the clinical management of HIV infection. This conclusion is highly relevant to the underlying premise of immunomodulator Dzherelo and two therapeutic AIDS vaccines in this issue which also have shown positive clinical results and which incidentally also function through induction of immune tolerance rather than immune activation.

Paper by Vichai Jirathitikal and Aldar S. Bourinbaiar describes pre-clinical and safety studies of their therapeutic AIDS vaccine, V-1 Immunitor (V1), derived from the blood of HIV-positive donors and formulated as a pill. Their study demonstrates that extensive chemical, in vitro and in vivo tests have failed to reveal any signs of toxicity. The manufacturing process that includes robust chemical- and heat-inactivation steps, completely inactivates HIV and other adventitious agents present in blood. The original source of V1 is the same as in Abalaka's vaccine. This perhaps explains why his and at least four other similar blood-derived vaccines have consistently shown beneficial effect when used as therapeutic modalities in AIDS patients. Over the last six years over 70,000 individuals in more than 68 countries have used V1 without a single incident of serious adverse reaction. It can be concluded that V1 is safe and its potential risk to cause toxicity or adverse events is negligible compared to the clinical benefit.

Dr. Amir Maksyutov and his team at the State Research Center of Virology and Biotechnology VECTOR, in Novosibirsk, Russia have developed a unique bioinformatics tool that allows identifying potentially harmful epitopes on vaccine's antigens. They screened Ebola virus proteins against almost half of known human proteins for the presence of so-called 'local similarities' – a term that refers to resemblance of structural patterns of unrelated proteins as a function of their amino acid composition. The Filoviridae virus family comprises the Marburg viruses, first identified in fatal hemorrhagic fever outbreaks in 1967 and the Ebola viruses – discovered a decade

later. While experimental Ebola vaccines have shown protection in animals, a human vaccine is yet to be discovered. Maksyutov et al., indicate that such a vaccine must be void of immunogenic regions that mimic host proteins. In contrary case adverse events, such as autoimmunity, may occur due to immune cross-reaction. Maksyutov, who is currently with AvaxisBio company, has applied this principle to a variety of other vaccines that is, HIV, influenza and smallpox. The smallpox vaccine project is now being pursued in collaboration with the MDM Group Inc., based in California.

The burden of respiratory infections in children and adults is very high, especially in developing countries. At least 1.9 million children died from acute RTIs in 2000, 70% of them in Africa and Southeast Asia. As current therapies of these frequently recurring infections have substantial limitations, preventive measures deserve priority. The review by Marit Meredith and Carlo Chiavaroli from OM Pharma in Switzerland describes orally formulated 'immunomodulator' OM-85 consisting of lyophilised extract from eight species of bacteria, which commonly cause respiratory tract infections, that is, *Haemophilus influenzae, Diplococcus pneumoniae, Klebsiella pneumoniae, Klebsiella ozaenae, Staphylococcus aureus, Streptococcus pyogenes, Streptococcus viridans and Moraxella catarrhalis*. They describe its efficiency and safety, pharmacoeconomic studies, and clinical trials conducted in children, in adults suffering from chronic obstructive pulmonary disease, and in special patient populations. OM-85 is affordable even in developing countries and is sold as an immunomodulator. However, by definition OM-85 is a multivalent oral bacterial vaccine, not much different from Silin's oral *Actinobacillus pleuropneumoniae* vaccine or Jirathitikal's tableted AIDS vaccine, the latter in fact has been licensed in Thailand and some African countries as a food supplement.

India has more than 5 million people infected with HIV-1 and this number is likely to increase in coming years. More than 90% of these infections are due to subtype C. Therefore, it is imperative that a vaccine be designed against local circulating subtype. Dr. Pradeep Seth reviews his own work on the development and immunogenicity testing of recombinant DNA and recombinant vaccinia-based (rMVA) vaccine candidates in animal models under Jai Vigyan Mission program of the Department of Biotechnology, Government of India. While his effort and results are impressive, Dr. Seth now encounters the same problem as his colleagues in South Africa or Nigeria. The scarcity of public funds for promoting biotechnology in developing countries seems to be a common problem. Unless scientists find ingenious ways to cope with that there is not much that can be done but to wait for an 'angel' – a biotechnology term for private investment.

Dr. Dmytro Silin, originally from Ukraine, spent several years in Taiwan where he and his Chinese colleagues worked on development of an oral *Actinobacillus pleuropneumoniae* vaccine. This pathogen triggers porcine contagious pleuropneumonia characterised by hemorrhagic pneumonia and fibrinous pleuritis with a high incidence of mortality. They observed that orally administered vaccine induces tolerance to challenge pathogen – a phenomenon commonly seen with these types of vaccines since early 20th century. They, however, were able to develop means to overcome tolerance. Their finding represents a genuine breakthrough and may become a highly promising approach of improving oral vaccine potency. It is clear that in the next five–ten years, new vaccines and new vaccine delivery technology will appear that will fundamentally change they way we prevent and treat diseases. Oral vaccine as affordable and simple delivery will be on top of the of priority list.

Professor Thomas Tallberg, the Director of the Institute for Bio-Immunotherapy in Helsinki, Finland is internationally respected, a forty-year veteran in cancer research and nutritional supplements. His autologous cancer vaccine first developed in 1967 at the Institute Pasteur has been successfully used during last 40 years on hundreds of patients. Today, the notion of therapeutic cancer vaccines has become widely accepted – almost every second biotech company claims developing one. Back then, Tallberg was one of the few pioneers. He is, however, not satisfied with the single-focused approach prevalent in the biotech industry, his flamboyance leads him further or one could say "farther away from the pack". I have defended to leave his paper largely unedited against Reviewers' calls to the contrary. I felt that given his pioneering effort he might have ideas that others hadn't even started thinking about. After all, 40 years ago no one took seriously his idea of treating cancer with a vaccine. Who knows, paradigms do shift, and usually the ideas that were opposed most fiercely end up prevailing. Only time can decide whether or not he is right.

To conclude, I do hope that Readers will learn something new after reading presented papers or at least they will have a pause to contemplate. This special issue concerns vaccines in their myriad faces – some familiar, some unknown and some too good to be true. In any event as a Guest Editor for this issue I am thankful to the Editors, Drs. Calestous Juma and Mohammed Dorgham, for kindly offering me this opportunity and for their support and patience. I am entirely responsible for any error or mistake that may have occurred during preparation of this issue.