Human Vaccines & Immunotherapeutics: news

The continued development of COVID-19 vaccines

The most advanced candidate for SARS-CoV-2 vaccine, the mRNA vaccine mRNA-1273 (Moderna), has initiated a Phase 2 trial, in which safety and immunogenicity of two doses one month apart are being tested in 600 healthy adults split into two cohorts (<55 years and ≥55 years old). The placebo-controlled study will investigate two dosage levels. The vaccine was granted the Fast-Track Designation by the U.S. Food and Drug Administration (FDA).

A nanoparticle protein vaccine, NVX-CoV2373 (Novavax), administered with the saponin-based Matrix-M adjuvant, has entered a randomized, placebo-controlled Phase 1/2 trial, in which safety and immunogenicity of two dosage levels are being tested in 30 healthy adults.

The adenovirus-based vaccine (CanSino) was well tolerated and induced neutralizing antibody and T-cell responses in 108 healthy adults.1 Participants with pre-existing antibodies against the Ad5 vector showed reduced seroconversion. The vaccine is poised for a Phase 2 trial, which also will enroll elderly subjects.

Another adenovirus-vectored vaccine, ChAdOx1 nCoV-19 (AstraZeneca and Oxford University), failed to protect rhesus macaques from infection, but it did ameliorate the course of the disease and prevented viral pneumonia, which seen in 2/3 of unvaccinated monkeys.2

All above-mentioned vaccines target the SARS-CoV-2 spike (S) protein.

Atezolizumab was approved in U.S. for two indications

The PD-L1 inhibitor avelumab (Bavencio, Pfizer & Merck) extended median survival by 50% to 21 months in subjects with locally advanced or metastatic urothelial carcinoma. 700 patients, enrolled to the Phase 3 Javelin Bladder 100 trial following first-line chemotherapy treatment, were randomized to receive supportive care alone or together with avelumab every two weeks. 11% of patients had to discontinue avelumab due to adverse events.

“We saw a meaningful reduction in the risk of death and a significant overall survival benefit with avelumab, which underscores the potential for this immunotherapy to be practice-changing for patients. This highlights the potential benefits of a maintenance approach with avelumab in patients to prolong their lives following chemotherapy,” lead author Thomas Powles of Barts Cancer Institute said.

There are over half a million annual cases of bladder cancer globally. Subjects with metastatic disease have few treatment options.

New meningococcal conjugate vaccine was approved in the U.S.

The FDA has approved the quadrivalent meningococcal vaccine (MenCV) MenACYW-TT (MenQuadfi, Sanofi) for prevention of meningococcal invasive disease in people aged 2 years and older. The vaccine was shown in clinical trials to be safe and efficacious in vaccine-naive subjects and as a booster to other MenCVs.

Meningococcal meningitis is an acute and serious condition with 10-15% case-fatality rate and long-term complications. MenACYW-TT becomes the only MenCV approved for the elderly.
**Pembrolizumab doubles survival in aggressive bowel cancer**

The PD-1 inhibitor pembrolizumab (Keytruda, Merck) extended survival of metastatic microsatellite-instability-high bowel cancer patients to 16 months compared to 8 months in subjects treated with chemotherapy. Half of the patients in the experimental cohort reported no disease progression after two years compared to 19% in the chemotherapy arm. Pembrolizumab also induced complete remission in 11% of subjects.

The KEYNOTE-177 study, which enrolled 300 people from 23 countries, also found that serious adverse events were less likely following immunotherapy.

“Whilst only around 5% of advanced bowel cancer patients have [microsatellite] genetic mutations, they usually have a worse prognosis, and less response to chemotherapy and other targeted agents,” the trial’s UK investigator Kai-Keen Shiu of University College London said. “The results from this trial really are game-changing and will almost certainly result in a paradigm shift in our current clinical practice.”

**Cell immunity-inducing HIV vaccine protected monkeys from infection**

A novel vaccine regimen eliciting T-cell responses provided protection in a macaque model of HIV. The animals received an Env trimer vaccine designed to induce neutralizing antibodies and adjuvanted with TLR7/8 ligand nanoparticles, either alone or together with a novel vaccine based on the Gag protein encoded by a heterologous viral vector. A third group received adjuvant only.

The vaccines were administered in several doses over 18 months, after which the monkeys were challenged with SHIV in ten weekly exposures. In animals that received both vaccines, lower levels of neutralizing antibodies were sufficient for protection. Notably, they were also more protected in a second challenge after 20 weeks.

“All licensed vaccines to date work by inducing antibodies that neutralize a virus. But inducing and maintaining a high enough level of neutralizing antibodies against HIV is a demanding task,” senior author Bali Pulendran of Stanford University said. “We’ve shown that by stimulating the cellular arm of the immune system, you can get stronger protection against HIV even with much lower levels of neutralizing antibodies.”

**New vaccine strategy protects mice from malaria**

A ‘prime and trap’ vaccination approach induced protective immunity against liver-stage malaria in a preclinical study. T cells are first activated in the spleen with the ribosomal L6 protein from *Plasmodium berghei*, and then trapped in the liver to form resident memory cells. A single vaccine dose provided lasting protection from sporozoite challenge in a mouse model of malaria.

There is still no highly protective vaccine to the disease that causes 200 million cases and 500,000 deaths annually, many of them in young children.

**Coxsackie virus vaccine passes preclinical tests**

An inactivated Coxsackie B vaccine induced neutralizing antibody responses against all six known strains in mice and non-human primates. The enteric virus causes the common cold, but sometimes also more serious conditions, such as myocarditis and meningitis. It has been implicated in the development of type 1 diabetes, and results from the study show that the vaccine prevented virus-induced diabetes in a mouse model.

The vaccine is ready for clinical trials with the hope that it can be administered to children with genetic predisposition to type 1 diabetes.

**References**

1. Zhu FC, Li YH, Guan XH, Hou LH, Wang WJ, Li JX, Wu SP, Wang BS, Wang Z, Wang L, Jia SY, Jiang HD, Wang L, Jiang T, Hu Y, Gou JB, Xu SB, Xu JJ, Wang XW, Wang W, Chen W. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. Lancet 2020; S0140-6736(20)31208-3
2. van Doremalen N, Lambe T, Spencer A, Belij-Rammerstorfer S, Purushotham JN, Port JR, Avanzato V, Bushmaker T, Flaxman A, Urszewska M, Feldmann F, Allen ER, Sharpe H, Schulz J, Holbrook M, Okumura A, Meade-White K, Pérez-Pérez L, Bissett C, Gilbride C, Williamson BN, Rosenke R, Long D, Ishwarbhai A, Kailath R, Rose L, Morris S, Powers C, Lovaglio J, Hanley PW, Scott D, Saturday G, de Wit E, Gilbert SC, Munster VJ. ChAdOx1 nCoV-19 vaccination prevents SARS-CoV-2 pneumonia in rhesus macaques. BioRxiv doi: 10.1101/2020.05.13.093195
3. Arunachalam PS, Charles TP, Joag V, Bollimpalli VS, Scott MKD, Wimmers F, Burton SL, Labranche CC, Petitdemange C, Gangadhara S, Styles TM, Quarnstrom CF, Walter KA, Ketas TJ, Legere T, Jagadeesh Reddy PB, Kasturi SP, Tsai A, Yeung BZ, Gupta S, Tomai M, Vasilakos J, Shaw GM, Kang CY, Moore JP, Subramaniam S, Khatri P, Montefiori D, Kozlowski PA, Derdeyn CA, Hunter E, Masopust D, Amara RR, Pulendran B. T cell-inducing vaccine durably prevents mucosal SHIV infection even with lower neutralizing antibody titers. Nat Med 2020; doi: 10.1038/s41591-020-0858-8
4. Valencia-Hernandez AM, Ng WY, Ghazanfari N, Ghilas S, de Menezes MN, Holz LE, Huang C, English K, Naung M, Tan PS, Tullert KM, Steiner TM, Enders MH, Beattie L, Chua YC, Jones CM, Cozjinsen A, Molland V, Cai Y, Bowen DG, Purcell AW, La Gruta NL, Villadangos JA, de Koning-Ward T, Barry AE, Cockburn IA, McFadden GI, Graz S, Lahoud MH, Bertolino P, Schittenhelm RB, Caminschi I, Heath WR, Fernandez-Ruiz D. A Natural Peptide Antigen within the Plasmodium Ribosomal Protein RPL6 Confers Liver TRM Cell-Mediated Immunity against Malaria in Mice. Cell Host Microbe 2020; 6736(20)31208-3
5. Stone VM, Hankaniemi MM, Laitinen OH, Sioofy-Khojine AB, Lin A, Diaz Lozano IM, Mazur MA, Marjomäki V, Loré K, Hyötty H, Hytönen VP, Flodström-Tullberg M. A hexavalent Coxsackievirus B vaccine is highly immunogenic and has a strong protective capacity in mice and nonhuman primates. Sci Adv 2020; 6(19):eaaz2433