VOLUME 7, ISSUE 3 SEPTEMBER 2020

Drug and Poison Information Center Bulletin

Faculty of Pharmacy

Tanta University

In this issue

New updates from ESC-guidelines for diabetes.

What's new about COVID-19 vaccination?

Research area *New*

Hydrogels for neural tissue restoration

Rapamycin..an "anti-aging' drug

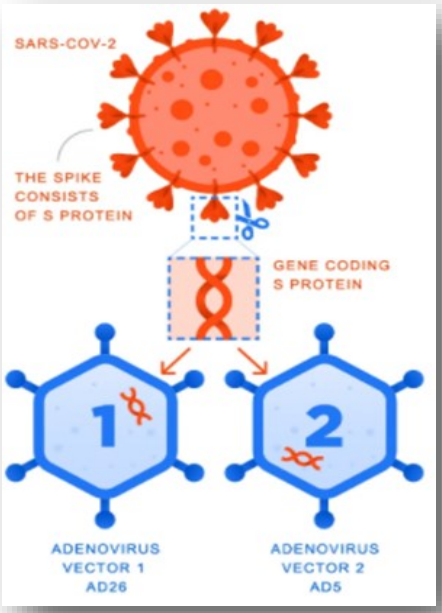
Are we expecting a COVID-19 vaccine soon?

It is almost 9 months now since the first diagnosis of a coronavirus-diseases (COVID-19) case in Hubei province in China. Since then, the whole world is suffering from the devastating effects . Besides being a health crisis that affects billions of people in the 7 continents, the pandemic is causing broader consequences for economies, societies, labor market, way of living and global relations. These effects will be long term and we still do not know when we will recover from it. Between a 30 million confirmed-case, more than 800 thousand deaths worldwide till now and fears of a new spike in cases next winter. Scientists are trying to holdout waiting for a vaccine that we hopefully put an end to the pandemic. Nearly, all top pharmaceutical companies and labs are in a race to produce the first safe and effective vaccine for COVID-19 and here are some highlights of what is on the table:

1-Sputnik V:

On August 11, the Russian Ministry of Health has registered a vaccine and became the first registered COVID-19 vaccine on the market under the name of Sputnik V. It is an adenovirus vector-based vaccine where the gene from adenovirus, which causes the infection, is removed while the gene coding S protein from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is inserted. This inserted element is safe for the body but still helps the immune system to react and produce antibodies.

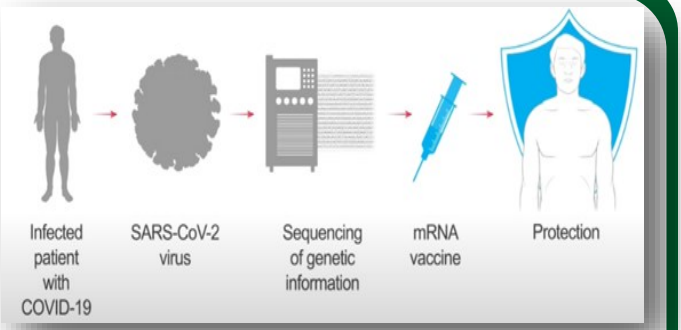
Human adenoviruses are considered as some of the easiest to engineer in this way and therefore they have become very popular as vectors. The vaccine depends on 2 adenovirus vectors AD26 and AD5. After first vaccination with AD26, the body will synthesize S protein in response, where the production of immunity begins. Second vaccination after 21 days with AD5, which is another vector unknown to the body, this will boost the immunity and provide long-lasting immunity. Phase 1 and 2 clinical trials of the vaccine have been completed on August 1, 2020 and the results were published in THE LANCET on September 4, 2020. The vaccine has induced a strong humoral and cellular immune response and no unwanted side effects were observed. The vaccine induced strong antibody and cellular immune response. Phase 3 clinical trials involving more than 40,000 people in Russia has started on August 24. Several countries, such as United Arab Emirates (UAE), Saudi Arabia and Philippines will join the clinical trials of Sputnik V locally.



2-Moderna vaccine (mRNA-1273 vaccine):

mRNA-1273 is an mRNA vaccine against COVID-19 encoding the Spike (S) protein, the sequence for this protein was isolated from the genetic information of the virus. The mRNA is administered directly to the patient as a vaccine.

The mRNA is taken by immune cells, where a copy of S protein is made as if the cells has infected by the corona virus. Other immune cells identify S protein and then develop protective immune response if the person gets infected with the virus later. **On February 24,** Moderna therapeutics incorporation with US national institutes of health (NIH) started phase 1 clinical trial on the vaccine.



In the trial a two-dose vaccination schedule of mRNA-1273 given 28 days apart was able to induce rapid and strong immune responses against SARS-CoV-2. mRNA-1273 was generally safe and well-tolerated, with no serious adverse events reported. The results of Phase 1 trials and non-human primates is published in New England Journal of Medicine. **On July 27,** The Phase 3 study of mRNA-1273 started on a 30 thousand participant to assess the ability of vaccine to prevent the infection with COVID-19 in adults ≥ 18 years.

3-ChAdOx1 nCoV-19 vaccine (AZD1222):

We talked in the last issue (Vol.7 issue 2) about the vector-vaccine AZD1222 or what is publicly known as AstraZeneca/Oxford vaccine. On August 15, the results of phase 1/2 trials were published in The Lancet. The vaccine was given as a single dose and no serious adverse reactions occurred, only mild or moderate ones. One group received a booster dose after 28 days. The vaccine was able to induce strong humoral and cellular immunity resulted in marked increases in SARS-CoV-2 spike-specific effector T-cell responses as early as day 7, peaking at day 14. AstraZeneca started the Phase 3 clinical trial on August 17, with a 30 thousand participant. The trial will be randomized, double blind, placebo-controlled trial where participants will receive 2 IM doses separated by 28 days to assess the safety, tolerability and ability of the vaccine to prevent COVID-19 infections in adults ≥ 18 years.

There are also other promising vaccines like the Chinese private company Sinovac Biotech vaccine that was given an emergency approval for limited use on July from the Chinese government after successful phase 1/2 trials. Also, the mRNA vaccine produced by the collaboration between Pfizer and BioNTech started its phase 2/3 trials on July 27, with 30 thousand participants. We are all hoping that any of them succeed soon.

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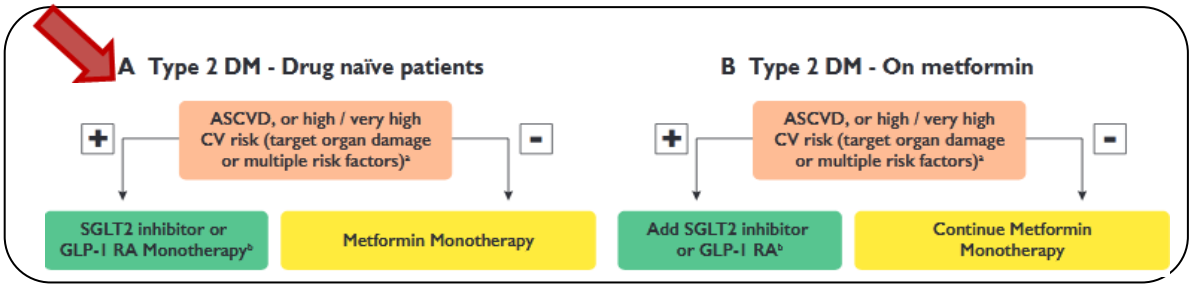
By: Mohamed K. Talaat, PharmD.

For cardio-protection issues, are drugs from SGLT2 inhibitors and GLP-1RAs competing with metformin on the 1st line therapy position?

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality in patients with type 2 diabetes (T2D). In the past few years, several drugs from the antihyperglycemics; sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonist (GLP-1RA) classes have been shown to have important effects in reducing myocardial infarction, stroke, heart failure, diabetic kidney disease, and death from CVD. Current American Diabetes Association (ADA) guidelines continue to recommend metformin as first-line therapy for glucose-lowering in patients with T2D. In contrast, the recent European Society of Cardiology (ESC)/European Association for the Study of Diabetes (EASD) guidelines now recommend the starting with an SGLT2 inhibitor or GLP-1RA (with proven cardioprotective effects) before metformin in newly diagnosed T2D patients who have established CVD or are at very high CVD risk.



Part of the treatment algorithm of T2D according to the 2019 ESC/EASD guidelines.

The New 2020 American College of Cardiology (ACC) Guidance on CVD Risk Reduction in Diabetes summarized important issues of SGLT2 inhibitors' and GLP-1RAs' drug monographs as the following:

SGLT2			
	Canagliflozin	**Dapagliflozin**	**Empagliflozin**
Doses for CV benefit	100 mg PO daily	10 mg PO daily	
Indications	**Improve glycemic control in adults with T2D as an adjunct to diet and exercise.**		
	• ↓risk of MI, stroke, or CV death in adults with T2D + CVD • ↓the risk of ESRD, doubling of serum creatinine, CV death, and hospitalization for HF in patients with T2D + diabetic nephropathy + albuminuria	• ↓the risk of hospitalization for HF in adults with T2D + CVD or CV risk factors • ↓the risk of CV death and hospitalization for HF in adults with HFrEF	Reduce risk of CV death in adults with T2D + CVD
Use according to eGFR in ml/min/1.73 m^2	<30: use is not recommended	• <45: use is not recommended • <30: use is contraindicated	<45: use is not recommended

Contraindications	History of serious hypersensitivity reaction to drug, pregnancy or breastfeeding, on dialysis, eGFR <30 mL/min/1.73 m^2 (dapagliflozin), ESRD (dapagliflozin and empagliflozin) , and severe renal impairment (empagliflozin).
Cautions	• Discontinue at least 3 days before a planned surgery to prevent postoperative ketoacidosis. If HbA1c well-controlled at baseline, or known history of frequent hypoglycemic events, wean or stop sulfonylurea or glinide and consider reducing total daily insulin dose by ≈20% when starting therapy. • May contribute to intravascular volume contraction; consider stopping or reducing diuretic dose if applicable. • Patients with prior amputation, severe peripheral neuropathy, severe peripheral vascular disease, or active diabetic foot ulcers or soft tissue infections. • Possible increased risk of bone fractures (canagliflozin).
Adverse effects to monitor	Genital fungal infections, urinary tract infections, euglycemic diabetic ketoacidosis, lower limb ulcerations, and soft tissue infections.

GLP-1RAs						
	Dulaglutide	**Exenatide QW**	**Liraglutide**	**Lixisenatide**	**Semaglutide SC**	**Semaglutide PO**
Recommended doses for CV benefit	▪ Initiate 0.75 mg SC/week ▪ Titrate slowly to 1.5 mg	2 mg SC/ week	▪ Initiate 0.6 mg SC daily ▪ Titrate slowly to 1.8 mg.	▪ 10 mcg SC daily ▪ Titrate as tolerated to 20 mcg daily based on prescribing information	▪ Initiate 0.25 mg SC/week ▪ Titrate slowly to 1 mg once weekly	▪ Initiate 3 mg PO/day for the first month ▪ Titrate slowly to 14 mg daily
Indications	**Improve glycemic control in adults with T2D.**					
	↓MACE for people with T2D with and without CVD		↓risk of MI, CVA, or CV death in adults with T2D + CVD		↓risk of MI, CVA, or CV death in adults with T2D + CVD	
Dose modifications	▪ Up-titrate slowly to ↓nausea and vomiting. ▪ No dose adjustment necessary with renal or hepatic impairment; data in ESRD are limited	eGFR <45 mL/min/1.73 m^2 use is not recommended	▪ Up-titrate slowly to ↓nausea and vomiting ▪ No dose adjustment is necessary with renal or hepatic impairment	▪ Up-titrate slowly to ↓nausea and vomiting ▪ eGFR 15 to 29 mL/min/1.73 m^2: use caution and monitor renal function. ▪ eGFR <15 mL/min/1.73 m^2: use is not recommended	▪ Up-titrate slowly to ↓nausea and vomiting ▪ No dose adjustment is necessary with renal or hepatic impairment	
	Discontinue if pancreatitis is suspected and do not restart if pancreatitis is confirmed.					

Contra-indications	• History of serious hypersensitivity reaction to drug. • Pregnancy or breast feeding. • Severe renal impairment or ESRD (exenatide, lixisenatide). • Personal or family history of medullary thyroid cancer. • Personal or family history of MEN2.
Cautions	• Hypoglycemia risk increased with insulin, sulfonylureas, or glinides. • May delay gastric emptying; not recommended in patients with clinically meaningful gastroparesis. This effect is usually transient with longer-acting GLP-1RAs. • Patients with prior gastric surgery, including bariatric surgery. • Diabetic retinopathy complications were reported with semaglutide SC, while the causality assessment is uncertain.
Adverse effects to monitor	• Nausea, vomiting, diarrhea, headache, weakness, or dizziness. • Hypoglycemia when given with insulin, sulfonylureas, or glinides. • Weight loss. • Injection site reactions.

*CV= cardiovascular; CVA = cerebrovascular accident; CVD= cardiovascular disease; eGFR= estimated glomerular filtration rate; ESRD= end-stage renal disease; GLP-1RA = glucagon-like peptide-1 receptor agonist; HbA1c= hemoglobin A1c; HF= heart failure; HFrEF= heart failure with reduced ejection fraction; MACE = major adverse cardiovascular events; MEN2 = multiple endocrine neoplasia, type 2; MI = myocardial infarction; PO= "per os," by mouth; ; QW = once weekly; SC = subcutaneous; SGLT2= sodium-glucose cotransporter-2; T2D= type 2 diabetes. Because there is no evidence of a graded dose response regarding CV and renal effects, SGLT2 inhibitors with CV benefit should be initiated at the lowest dose tested in CV and renal outcomes trials. Those doses are listed here. No further dose titration is needed for CV or renal risk reduction. However, dose increases may provide further glucose reduction benefits if indicated. ** Or maximally tolerated dose based on prescribing information.*

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By: Bassant Maher, M.Sc.

Could rapamycin help humans live longer and healthier?

Sirolimus® (rapamycin) is a macrolide compound that inhibits T-lymphocyte activation and proliferation in response to antigenic and cytokine stimulation and inhibits antibody production. Rapamycin and its analog becoming an "anti-aging drug today".

Mechanism of action:

- It binds to FKBP-12, an intracellular protein, to form an immunosuppressive complex, which inhibits the regulatory kinase, mTOR (mechanistic/mammalian target of rapamycin). This inhibition suppresses cytokine mediated T-cell proliferation, halting progression from the G1 to the S phase of the cell cycle. It inhibits acute rejection of allografts, prolongs graft survival, and prevents the proliferation of lymphangioleiomyomatosis cells.
- Inhibitors of mTOR, including clinically available rapalogs such as rapamycin (Sirolimus) and Everolimus, are gerosuppressants, which suppress cellular deterioration due to aging. Rapamycin slows aging and extends life span in a variety of species from worm to mammals. Rapalogs can prevent age-related diseases, including cancer, atherosclerosis, obesity, neurodegeneration, and retinopathy and potentially rejuvenate stem cells, immunity and metabolism.

Dosing and Administration:

- The magnitude of life extension by rapamycin depends mostly on reaching a high peak blood level. It was suggested in 2008 that a pulse (intermittent) schedule of rapamycin administration would improve regeneration of stem cells while avoiding mTORC2 inhibition. For example, instead of daily administration, a weekly administration of a higher dose can be suggested to achieve a high peak blood level, followed by drug-free period to avoid undesirable effects.
- Still, everyday treatment of the elderly (1 mg/day for several weeks) was not associated with side effects and has been shown to be safe. Similar results were achieved with low doses of other mTOR inhibitors. Another option is an alternating schedule; for example, a 3-months course of weekly rapamycin alternating with a rapamycin-free month. Finally, anti-aging schedules can be very flexible to fit an individual patient.

Safety data:

- Rapamycin is not much more dangerous than ordinary drugs. The most worrying side effects of it have not been confirmed. At low doses, or when administered as a single high dose, no side effects have been detected so far in the elderly. At high doses, rapamycin and everolimus slow cell proliferation, which decreases blood cell counts. As a result, mild and reversible thrombocytopenia (low platelet count), anemia and leukopenia are their most common side effects. But a mild reduction of platelets may be beneficial.
- There are no known fatal cases of acute rapamycin (sirolimus) overdose. For example, in a failed suicide attempt, an 18-year-old woman ingested 103 mg of rapamycin tablets, and the only detected effect was an elevation in total blood cholesterol. In rats, rapamycin's LD50, a measure of drug lethality, could not be determined because it is higher than 2500 mg/kg. While a single dose of rapamycin is safe, it is sufficient to extend life and decrease obesity in several rodent models. Furthermore, transient treatment with rapamycin can be long lasting, extending the lifespan and preventing obesity long after drug discontinuation.

In conclusion, the side effects of rapamycin are well-known and reversible. When used on an anti-aging schedule, side effects may be absent but, if not, they may be mitigated by combining rapamycin with other anti-aging drugs (metformin, statins) or by temporarily discontinuing it.

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By: Mai Mousa, PharmD.

Upcoming conference in 2020

Research area

An area for new research ideas/points in different fields of pharmacy practice.

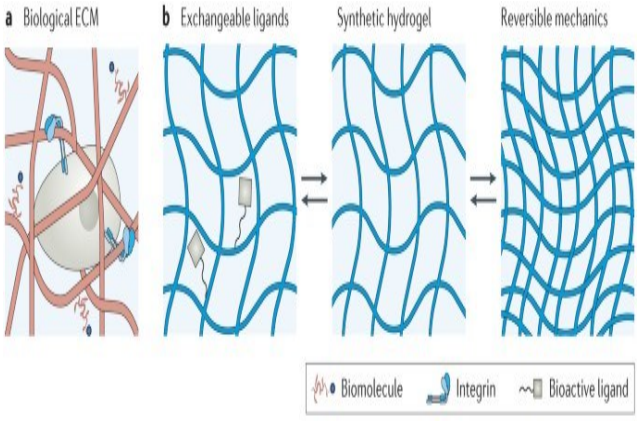
Implantable hydrogels for neural tissue restoration

Far Eastern Federal University (FEFU) scientists have developed implantable hydrogels based on plant polysaccharides (pectins). They can play the role of an artificial extracellular matrix, a special network of molecules that fills the space between body cells. The development to be used as a medium for growing tissues and organs, as well as for drug delivery and brain recovery after removal of malignant tumors glioblastoma.

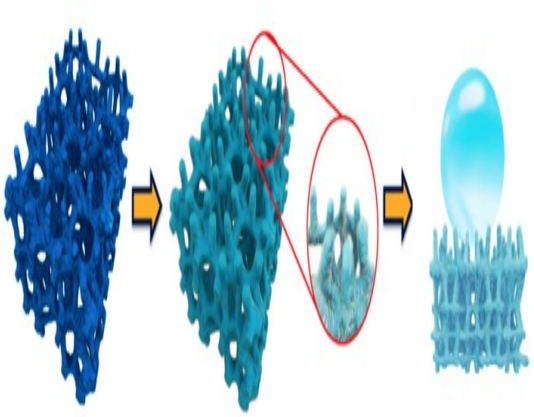
The hydrogels developed at the FEFU School of Biomedicine (FEFU SBM) are plant carbohydrate-based materials made of pectins modified by bioengineering methods. They are suitable for neural tissue restoration after its malignant transformation caused by brain tumors, and after damages caused by traumas or neurodegenerative diseases, involving such as cell death or loss of functional activity of cells and their environment.

The scientist explained that in the human body, the extracellular space is a complex molecular network, i.e. a matrix, which consists of two main components: protein and carbohydrate. The neural system matrix differs from the matrix of many other tissues because it has more carbohydrates and resembles “marshmallow” in its physicochemical properties. This vary from a more elastic and rigid matrix with a protein component predominance typical for connective tissues. It is almost impossible for cells to move along the carbohydrate matrix. The problem is that tumor cells control the rigidness of its extracellular space by adding protein components to it. By doing that, they pave a pathway for themselves to run away in order to metastasize and form new tumors in other areas of the body.

"Some variations of our extracellular hydrogel matrices are capable of suppressing the cell proliferation in glioma, a malignant brain tumor. Their chemical modifications can be used to secure the normal neural stem cells potential preserving them in an undifferentiated state, saving their viability and potential for the future."



"The matrix with a predominance of the carbohydrate component, implanted after the tumor was removed, will not only inhibit the growth and proliferation of cells, but will also be perfect as a delivery vehicle for highly toxic drugs." .



Such drugs will be released from it gradually, causing less harm to the body as a whole, and killing the remaining tumor cells. At the next stage, it is possible to stimulate the regeneration and growth of neural cells by implanting injection of a tougher matrix containing a large proportion of proteins into the operated area," says Vadim Kumeiko.

The scientist clarified the approach was proposed by his research group earlier in Frontiers in Bioengineering and Biotechnology, a new article is devoted to a partial experimental justification of the concept. In the future, scientists plan to investigate the effect of pectin matrix composition on the rate of drug release, and what combination of carbohydrate and protein components will allow restoring neural tissue without scars or excessive density typical for tumor tissue.

In general, so far there are very few materials in the world that are approved for neural tissue bioengineering and clinical practice. Mainly, they are intended for the regeneration of the peripheral rather than the central nervous system.

"This is interesting for the development of cellular biotechnologies in regenerative medicine, Certainly, bioengineering solutions associated with the use of extracellular matrices from pectins need to be carefully checked. However, we expect that in the future our hydrogels can be implanted in the brain tumor resection area in order to kill the tumor cells remaining after the operation." says Vadim Kumeiko.

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By: Marwa EL-Sayed, PGCPD.

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Vision

Improving healthcare services within the society through provision of evidence-based, unbiased, patient oriented drug information services & adverse drug reporting system.

Activities

- Answering drug information requests.
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