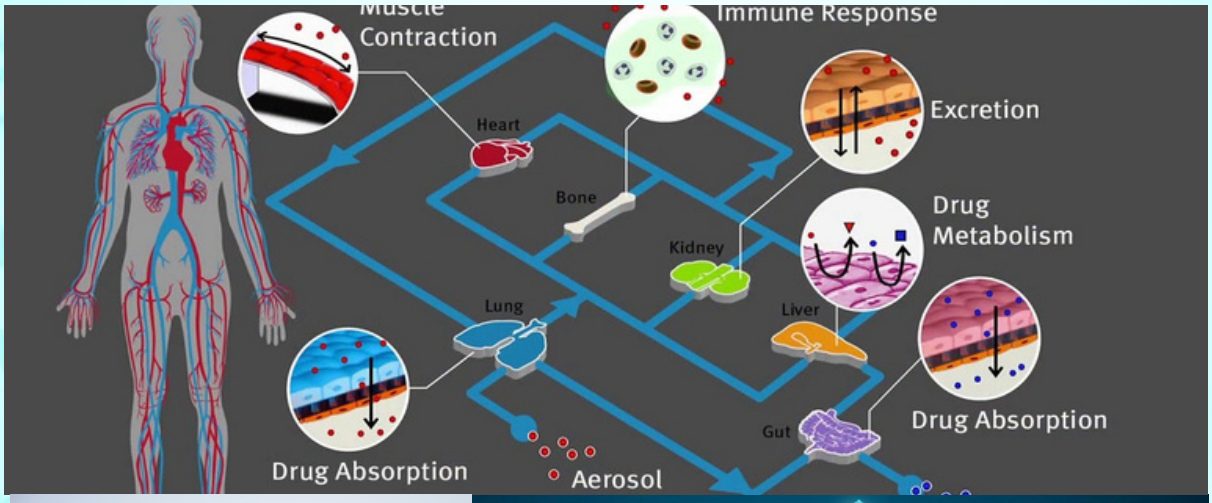
SPER NEWSLETTER



IN THIS EDITION:

We, at SPER, bring forward a one-step news for all.
Find out below what this specially curated the edition has in store for you-

- **Digital Therapeutics**
- **Biosimilars**
- **Organ On A Chip**

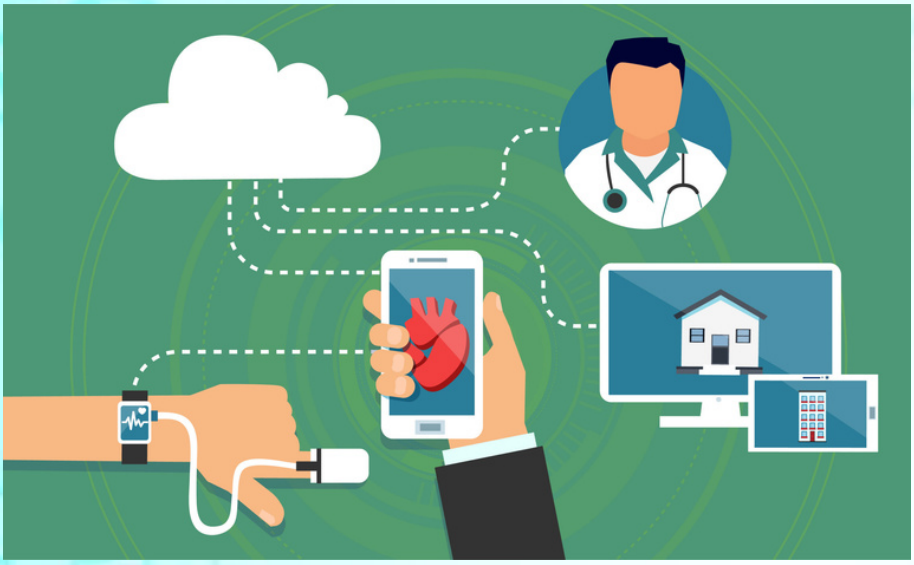
Digital Therapeutics

- With the rapid advancement of science and technology, every human being, including patients have been getting more empowered than ever before. As a result, it has become imperative to seek out digital health solutions.

- The pandemic's crippling impact has taught us that patients' self-awareness and voluntary participation in their treatment are now becoming a requisite. One such digital health solution is Digital Therapeutics (DTx).

- DTx is defined by the Digital Therapeutics Alliance (DTA) as "delivering evidence-based therapeutic interventions to patients that are driven by software to prevent, manage, or treat a medical disorder or disease." They can be used alone or in conjunction with medications, devices, or other therapies to improve patient care and health outcomes.

• HOW DTx WORKS?



- DTx is a collection of applications that assists in the treatment of disease by altering the patient's behavior and monitoring for improved and long-term outcomes.

- They may, for example, encourage the patient to follow: a specific diet, exercise routine, or medication regimen.

- DTx frequently targets conditions that are underserved by the healthcare system, such as chronic diseases or neurological conditions. Evidence also suggests that DTx can also be used to treat substance abuse.

HOW DTx IS DIFFERENT FROM WELLNESS APPS?

- The primary distinction between the two is that DTx is designed to target specific diseased conditions, most notably major chronic diseases like cardiovascular diseases such as hypertension, diabetes, and pulmonary diseases such as COPD. Wellness apps, on the other hand, take a broader approach to an individual's health.

SOME DIGITAL THERAPEUTICS THAT ALREADY HAVE FDA APPROVAL

- reSET from Pear Therapeutics is a 90-day prescription digital therapeutic (PDT) for substance use disorder (SUD). The Boston-based company also worked with Sandoz Inc., a division of Novartis, to receive FDA approval for reSET-O, a PDT for treating individuals with Opioid Use Disorder (OUD).

- Natural Cycles is a birth control app created by a Sweden-based company of the same name. It was approved by the FDA in 2018. This mobile app helps women track their fertility to prevent unwanted pregnancies via the rhythm method. The app analyzes data from past menstrual cycles and body temperature readings to determine when the user is most fertile. On the days the user is most likely to be ovulating, the app displays “Use Protection” on the mobile device’s screen.

- Apple, headquartered in Cupertino, Calif., received FDA clearance in 2018 for an electrocardiogram (ECG) app for its Apple Watch Series 4 that allows users to take an ECG from their wrist to detect irregular heart rhythms and atrial fibrillation (AFIB).

• DTx IN INDIA

- Many Indian pharma companies are now changing their strategies, business models, and product portfolios to better adapt to changing market dynamics. Companies have recognized the incredible value proposition provided by DTx services/products.

- It is thought that DTx services could reduce drug manufacturing costs while also adding value for insurers by allowing them to customize products based on the needs of the patients.

- However, DTx is still not widely used in India, and only a few companies are planning to invest and enter the DTx market. For example, an Indian pharmaceutical behemoth is attempting to simplify the management of cardiovascular diseases through the use of prescription drugs and AI-powered digital therapies.

Big Pharma Is Tying Up With Digital Therapeutics Providers

Pharmaceutical Company	Digital Therapeutic Provider	Deal Date	Agreement Details
Otsuka	proteus DIGITAL HEALTH	November 2017	Announce first FDA approval of a digital pill
Lilly	Livongo	January 2018	Enter strategic diabetes research collaboration
SANOFI VENTURES	CLICK THERAPEUTICS™	July 2018	Sanofi Ventures leads Click's $17M funding round
NOVARTIS	PEAR THERAPEUTICS	November 2018	Announce commercial launch of first-ever FDA-authorized prescription digital therapeutic
Otsuka	CLICK THERAPEUTICS™	January 2019	Otsuka agrees to pay Click up to $300M to collaborate on a new digital mental illness medicine

RELATIONSHIP B/W DIGITAL HEALTH, DIGITAL MEDICINE, & DIGITAL THERAPEUTICS

Digital Health

- Entities that engage consumers for wellness and health-related purposes by obtaining health data.
- Do not require clinical evidence.
- Do not meet the regulatory definition of a medical device and hence, does not require regulatory oversight.

Digital Medicine

- Evidence-based software and/or hardware products measuring human health.
- Require clinical evidence.
- Requirements for regulatory oversight vary.
- Products classified as medical devices require regulatory approval, while those used as a tool to develop other drugs, devices, or medical products require regulatory acceptance by the appropriate review division.

Digital Therapeutics (DTx)

- Products delivering evidence-based therapeutic interventions to prevent manage or treat a disease.
- Require clinical evidence well as data on real-world outcomes.
- All DTx products must be reviewed and cleared or certified by regulatory bodies as required to support product claims of risk, efficiency, and intended use.

THE APPLICATIONS OF DIGITAL THERAPEUTICS IN CHRONIC DISORDERS:

Diabetes:

- Digital therapeutics have the potential to deliver diabetes lifestyle medicine on a large scale. A 12-week study on the effects of a novel digital therapeutic, Fare Well, on hemoglobin A1c (HbA1c) and diabetes medication use found clinically meaningful reductions in HbA1c during the use of the Fare Well digital therapeutic. With increased app engagement, glycemic control has been managed to improve. In this widely dispersed sample, both engagement and retention were high.

Hypertension:

- Blood pressure reductions were observed in adults with hypertension who were using digital therapeutics. A majority of the participants in the study achieved clinically meaningful blood pressure reductions quickly. Participants with more severe hypertension at baseline showed greater improvement.

Pain medication:

- In pain medicines, DTx can be useful in a variety of ways.
- DTx can facilitate the collection of real-time pain data, that can provide valuable information to both doctors and patients. Wearable devices can continuously monitor and transfer real-time pain data to wirelessly connected databases.
- DTx can help patients more effectively to correct chronic pain-related lifestyle changes. The role of lifestyle factors in the development and maintenance of chronic pain diseases, as well as other chronic diseases, is frequently underestimated.
- DTx could be used in pain education programs. Patient education provides patients with accurate information about their pain, which can encourage them to participate actively ineffective treatments.

• BARRIERS IN THE ADOPTION OF DTx:

- Even though DTX entities provide significant solutions to poorly addressed conditions and have substantial evidence showing their clinical value, DTx entities have still not significantly managed to enter mainstream healthcare.
- The following are the two main barriers to broader adoption of DTx:

1. Difficulty distinguishing DTx from more general health and well-being applications in the general digital health market.
2. Uneven incentives in the healthcare environment.

• Future Prospects:

- The rapid growth in research into DTx over the past decade has resulted in the commercialization of evidence-based applications.
- The two promising areas associated with digital therapeutics technologies are curation platforms and innovation. Smart advisors, cognitive computing, biochips, efficient computing, tactile sensations, volumetric and holographic displays, and natural language questions are a few promising technologies that need a special place on the DTx roadmap.
- Considering the outreach of digital health technologies, Insider Intelligence claims that the global capabilities of DTx will be not $9 billion as predicted before, but $56 billion by 2025. Hence, pharmaceutical companies are likely to either actively cooperate with mature tech companies or buy DTx suppliers.
- Those in the market who hesitate to work with DTx are likely to miss out on tremendous opportunities.

Biosimilars

- Biosimilars are a new class of pharmaceutical products that are designed to be safe and effective in the same way as the reference, off-patent biological that is already on the market but they have minor differences in clinically inactive elements.

This implies that biosimilars:

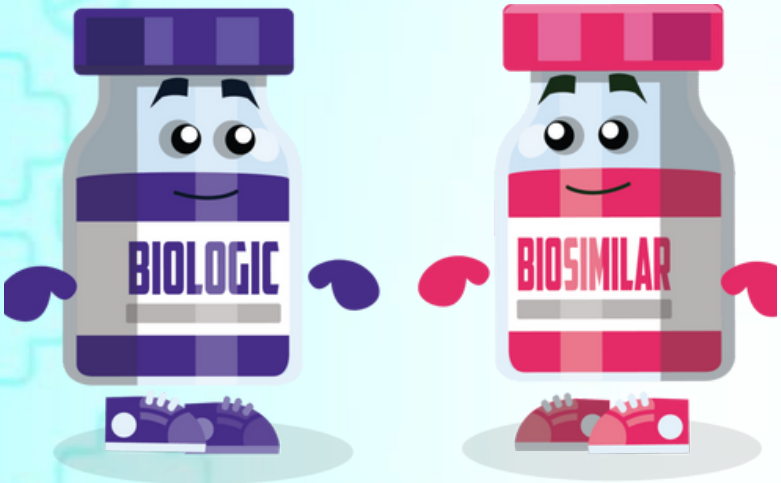
- Exhibits a similar route of administration as the original biologic.
- Poses the same strength as well as dosage form as the original biologic.
- Comprises the same possible side effects as the original one.
- Offers the same potential therapeutic advantages as the original biologic.

WHY ARE BIOSIMILAR DRUGS BEING DEVELOPED?

- Biologic drugs are often very expensive because they cost a lot to study and make. Their high cost can often make it hard for a person to use them, even if they might be the best treatment for a disease. To make biologic drugs more affordable and available to more people, Congress passed the Biologics Price Competition and Innovation Act (BPCIA). This act lets the FDA shorten the approval process for biosimilar drugs.
- Researchers and Congress think one benefit to biosimilar drugs is that they might lead to lower drug costs by offering patients more options for treatment. Some experts have estimated that biosimilar drugs could reduce the cost of biologics over time by many billions of dollars. But this depends on how many biosimilar drugs are tested, approved, and become available. It also depends on what types of diseases can be treated with biosimilar drugs and how much the approved drugs are used.

IF A BIOSIMILARS IS A BIOLOGIC, THEN WHAT IS A BIOLOGIC?

- A biologic drug (biologics) is a product that is derived from living organisms or contains components of a living organism. It consists of a wide variety of products that have been derived from humans, animals, or microorganisms by the virtue of biotechnology. Biologics consists of potent medications.
- Some examples of biopharmaceutical products and medicines which have been prepared from biological agents include:

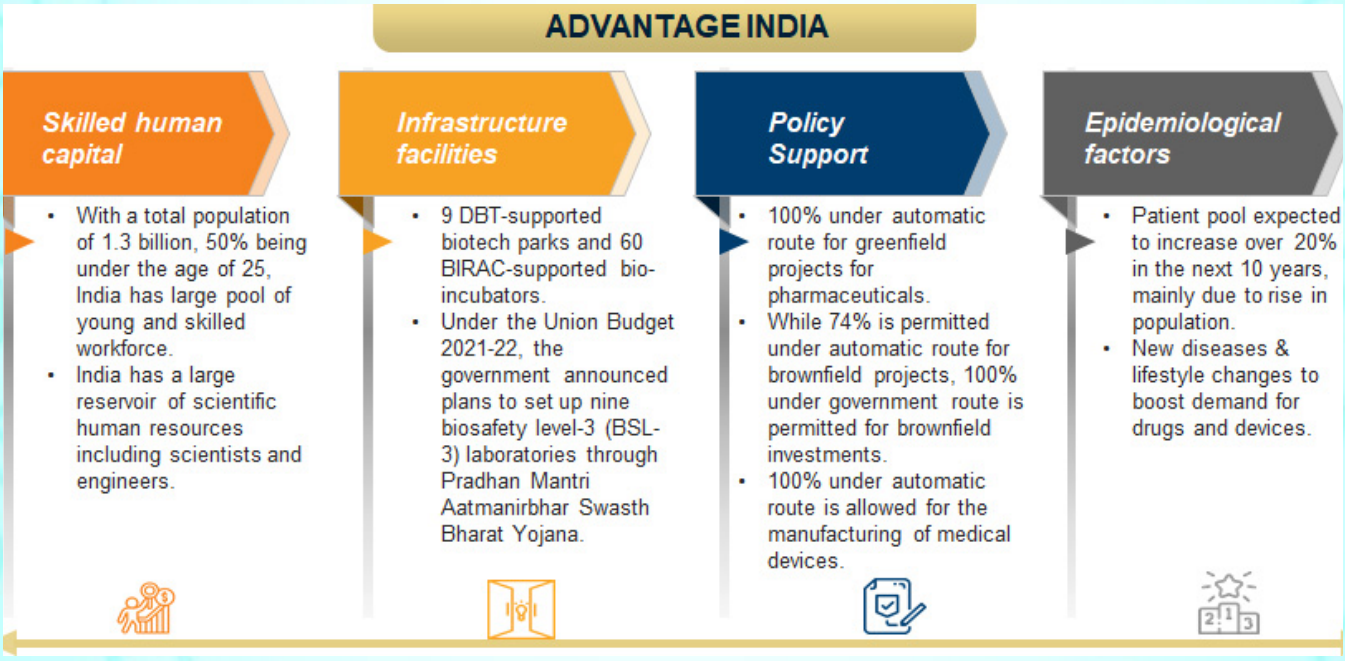


- Insulin for diabetes
- Vaccines
- Hormones for HRT and deficiencies
- Monoclonal antibodies
- Blood products and their transfusions
- Immunomodulators
- Enzymes
- Botox
- Gene therapy
- Cell signaling proteins.

- Today, there are over 200 biologics and vaccines on the market worldwide and the majority of these products are therapeutic proteins. These are proteins that are engineered in the laboratory for pharmaceutical use — Insulin was the first.
- Biosimilars were first approved for use in Europe in 2006 and very recently, in 2015 in the United States. India approved its first biosimilar as early as 2000. Now India leads with over 98 biosimilars approved by September 2019 (source: CDSCO).
- Approvals of biosimilars in regulated markets have further motivated Indian pharma companies to invest in the large and growing biosimilars market to increase their market share globally. Fulphila also became the first biosimilar developed in India to be commercialized in the US in 2019.
- Evidence shows that biosimilars offer significant cost savings to the healthcare system.
- A 20% reduction in the price of six off-patent biologics would save €1.6 billion, which would expand patient access

- **INITIATIVES BY THE GOVERNMENT OF INDIA TO PROMOTE BIOTECH-BASED DRUG DEVELOPMENT:**

The Government of India is keen to promote biotech-based drug development under the 'Make in India' campaign. Multiple reports have summarized initiatives introduced by the Department of Biotechnology (DBT), the Biotechnology Industry Research Assistance Council (BIRAC), and the government of India to support the vision of making India a hub for biotechnology-based innovation and research. These efforts focus on policy initiatives and investments, promotion of industry-institute collaborations, creating entrepreneurship cells to encourage biotech start-ups, and their development.



- AcE has mobilized more than INR 300 Crores for specific investments in the biotech innovation start-up ecosystem to scale-up R&D and innovation.
- The Department of Biotechnology (DBT) in collaboration with the World Bank, initiated an industry-academia collaborative mission 'National Bio-Pharma Mission' with a corpus of USD 250 Mn which is implemented by BIRAC.

- **HOW BIOSIMILARS ARE DIFFERENT FROM GENERIC DRUGS?**

Characteristic	***Biosimilars***	***Generics***
Chemical structure compared with the reference molecule	Complex molecules, post-translational modifications, slight differences in structure, same primary amino acid sequence	Simple molecules, well-defined structure, same amino acid sequence.
Immunogenicity	Can be immunogenic	No immunogenic potential
Manufacturing process	Complex biotechnological process	No need for complex modifications, easy manufacturing.
Time for marketing approval	7–8 years	2–3 years
Preclinical studies	Required	Not required, only bioequivalence studies
Regulation	Needs to demonstrate "similarity"	Needs to show bioequivalence

- **SOME INDIA-APPROVED DRUGS ARE GIVEN IN THE TABLE BELOW-**

Product name	***Active drug***	***Indications***
Glaritus	Insulin glargine	Diabetes mellitus
Grafeel	Filgrastim	Neutropenia
Epofer	Epoetin alfa	Anemia
Adfar	Adalimumab	RA, Crohn's disease
Erbitux	Cetuximab	Colorectal carcinoma
Krabeva	Bevacizumab	Colorectal cancer
Herceptin	Trastuzumab	Breast cancer
Intacept	Etanercept	RA
Abcixirel	Abciximab	Autoimmune disease
Relibeta	Interferon beta-1a	Multiple sclerosis

- **SOME FDA-APPROVED BIOSIMILAR PRODUCTS ARE GIVEN IN THE TABLE BELOW-**

Biosimilar Name	***Approval Date***	***Reference Product***
Releuko (filgrastim-ayow)	February 2022	Neupogen (filgrastim)
Yusimry (adalimumab-aqvh)	December 2021	Humira (adalimumab)
Rezvoglar (insulin glargine-aglr)	December 2021	Lantus (insulin glargine)
Byooviz (ranibizumab-nuna)	September 2021	Lucentis (ranibizumab)
Semglee (Insulin glargine-yfgn)	July 2021	Lantus (Insulin glargine)
Riabni (rituximab-arrx)	December 2020	Rituxan (rituximab)
Hulio (adalimumab-fkjp)	July 2020	Humira (adalimumab)
Nyvepria (pegfilgrastim-apgf)	June 2020	Neulasta (pegfilgrastim)
Avsola (infliximab-axxq)	December 2019	Remicade (infliximab)
Abrilada (adalimumab-afzb)	November 2019	Humira (adalimumab)
Ziextenzo (pegfilgrastim-bmez)	November 2019	Neulasta (pegfilgrastim)
Hadlima (adalimumab-bwwd)	July 2019	Humira (adalimumab)
Ruxience (rituximab-pvvr)	July 2019	Rituxan (rituximab)
Truxima (rituximab-abbs)	November 2018	Rituxan (rituximab)
Udenyca (pegfilgrastim-cbqv)	November 2018	Neulasta (pegfilgrastim)
Hyrimoz (adalimumab-adaz)	October 2018	Humira (adalimumab)
Nivestym (filgrastim-aafi)	July 2018	Neupogen (filgrastim)
Fulphila (pegfilgrastim-jmdb)	June 2018	Neluasta (pegfilgrastim)
Retacrit (epoetin alfa-epbx)	May 2018	Epogen (epoetin-alfa)
Ixifi (infliximab-qbtx)	December 2017	Remicade (infliximab

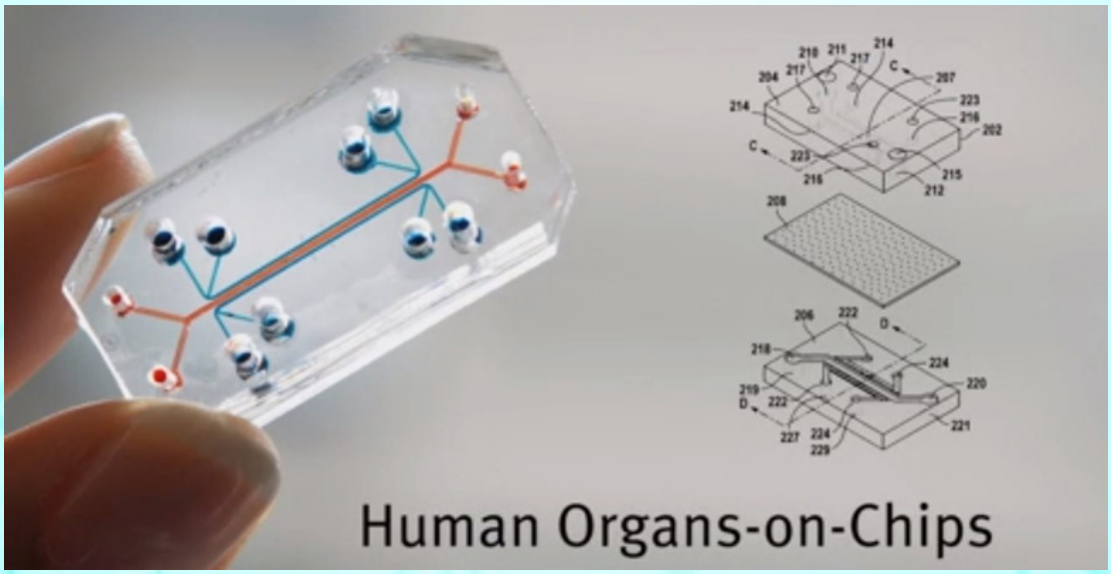
Ogivri (trastuzumab-dkst)	December 2017	Herceptin (trastuzumab)
Mvasi (Bevacizumab-awwb)	September 2017	Avastin (bevacizumab)
Cyltezo (Adalimumab-adbm)	August 2017	Humira (adalimumab)
Renflexis (Infliximab-abda)	May 2017	Remicade (infliximab)
Amjevita (Adalimumab - atto)	September 2016	Humira (adalimumab)
Erelzi (Etanercept-szzs)	August 2016	Enbrel (etanercept)
Inflectra (Infliximab-dyyb)	April 2016	Remicade (infliximab)
Zarxio (Filgrastim-sndz)	March 2015	Neupogen (filgrastim)
Zirabev (bevacizumab-bvzr)	June 2019	Avastin (bevacizumab)
Kanjinti (trastuzumab-anns)	June 2019	Herceptin (trastuzumab)
Eticovo (etanercept-ykro)	April 2019	Enbrel (etanercept)
Trazimera (trastuzumab-qyyp)	March 2019	Herceptin (trastuzumab)
Ontruzant (trastuzumab-dttb)	January 2019	Herceptin (trastuzumab)
Herzuma (trastuzumab-pkrb)	December 2018	Herceptin (trastuzumab)

OOAC{Organ On A Chip} Technology

• WHAT IS OOAC ?

An organ-on-a-chip (OOC) can be defined as a multi-channel 3-D microfluidic cell culture that has been integrated into a circuit (chip). Each organ chip, such as the lung, liver, intestine, or brain, is about the size of a AA battery.

- Without using humans or animals, these living, three-dimensional cross-sections of human organs provide a glimpse into their inner workings and the effects that medications can have on them.
- The organ chips have been devised to accurately re-establish the natural physiology as well as assess the mechanical forces which cells experience in the human body. The chips are lined with living human cells and their tiny fluidic channels reproduce blood and/or airflow just as in the human body. Their flexibility allows the chips to recreate breathing motions or undergo muscle contractions.
- Organ-on-a-chip technology (OOAC) is a physiological organ biomimetic system built on a microfluidic chip that is on the list of top ten emerging technologies.



• WHAT IS OOAC MADE OF?

- These microdevices are made of a translucent flexible polymer the size of a USB memory stick with hollow microfluidic channels coated with living human organ cells and blood vascular cells.
- Microfluidics, living cell tissues, stimulation, and sense are the four essential components of OOAC.

Microfluidics:

- The term microfluidics is described as the manipulation and processing of microscale fluids. In addition to generating fluid input/output during cell culture, microfluidics is employed to deliver target cells to a "pre-designated place."

Living Cell Tissue:

- Components that spatially align a specific cell type in the case of 2D or 3D systems.

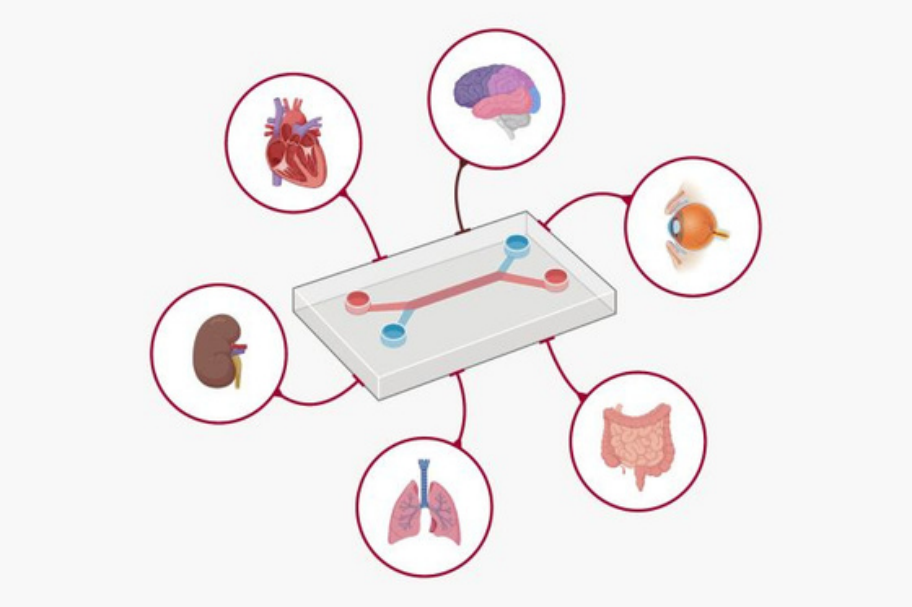
Stimulation::

- Both 2D and 3D cell cultures are used, while 3D cell cultures are better at simulating the in vivo milieu, 2D cell cultures are more cost-effective.

Sensing:

- It is a transparent chip-based visual function evaluation system. The model's overall functionality is assessed by this integrated component.

• EMERGING OOAC TECHNOLOGIES:



Liver OOAC:

- Evaluating the rate and extent of the first-pass metabolism of novel drugs.
- Assist in identifying drug metabolites and screening potential hepatotoxic agents.

Heart OOAC :

- Support 3D beating tissues from human cardiomyocytes.
- Ability to mimic Frank-Starling mechanics in cardiomyocytes.
- Display proper auxotonic contractions.

Lung OOAC :

- Evaluate the transport of drug molecules across epithelial cells found within alveoli.
- Mimic therapeutic delivery and transport in the lungs.

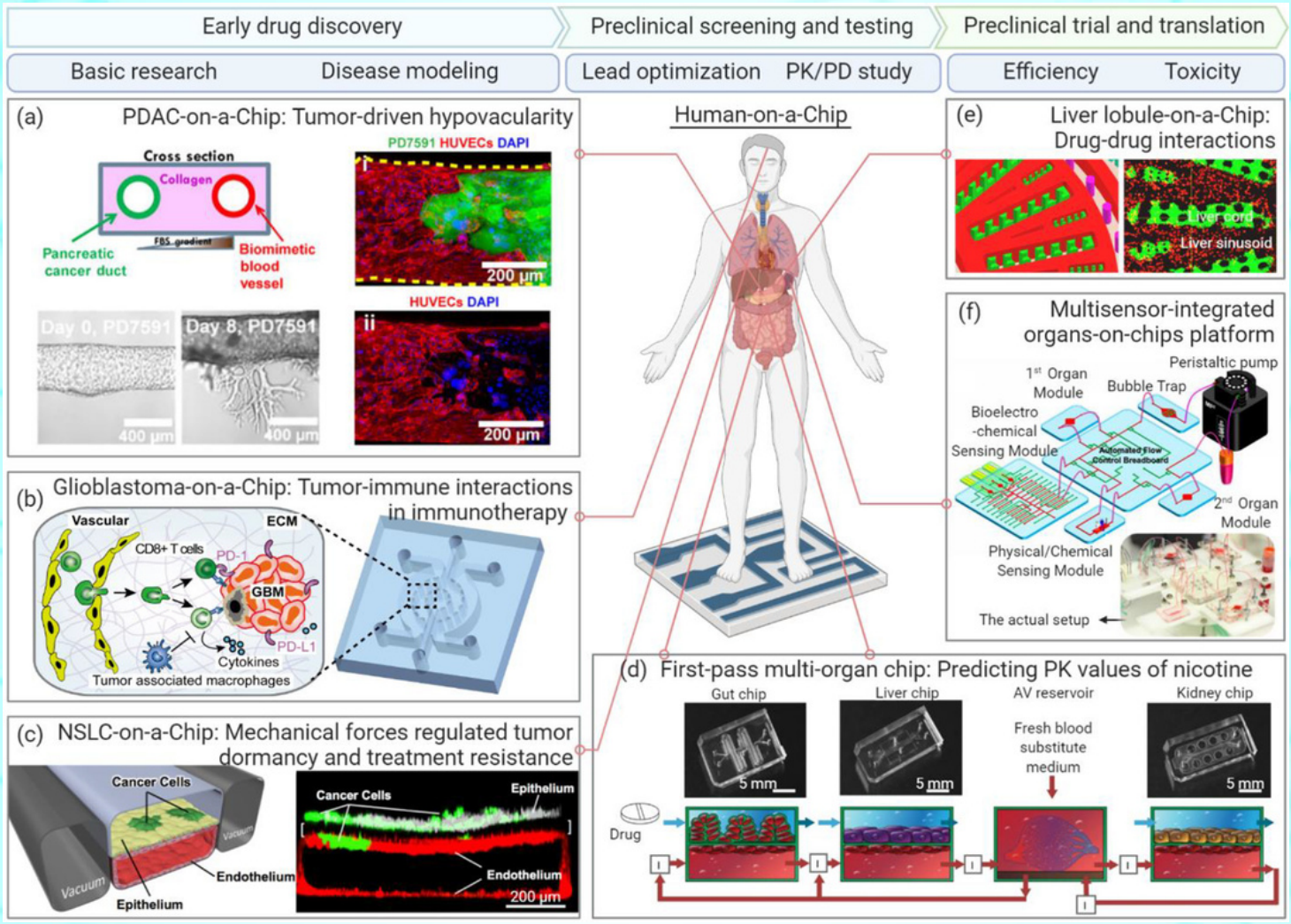
Intestine OOAC :

- Mimicking the fluidic dynamics and its peristaltic movement of the human intestine.
- Used to study drug transport, absorption, and toxicity studies.

Kidney OOAC :

- Microfluidics can stimulate the fluid environment that supports tubular cell growth and provides porous membrane support for the maintenance of cell polarity.

• ORGAN-ON-A-CHIP EMBRACES DRUG DEVELOPMENT

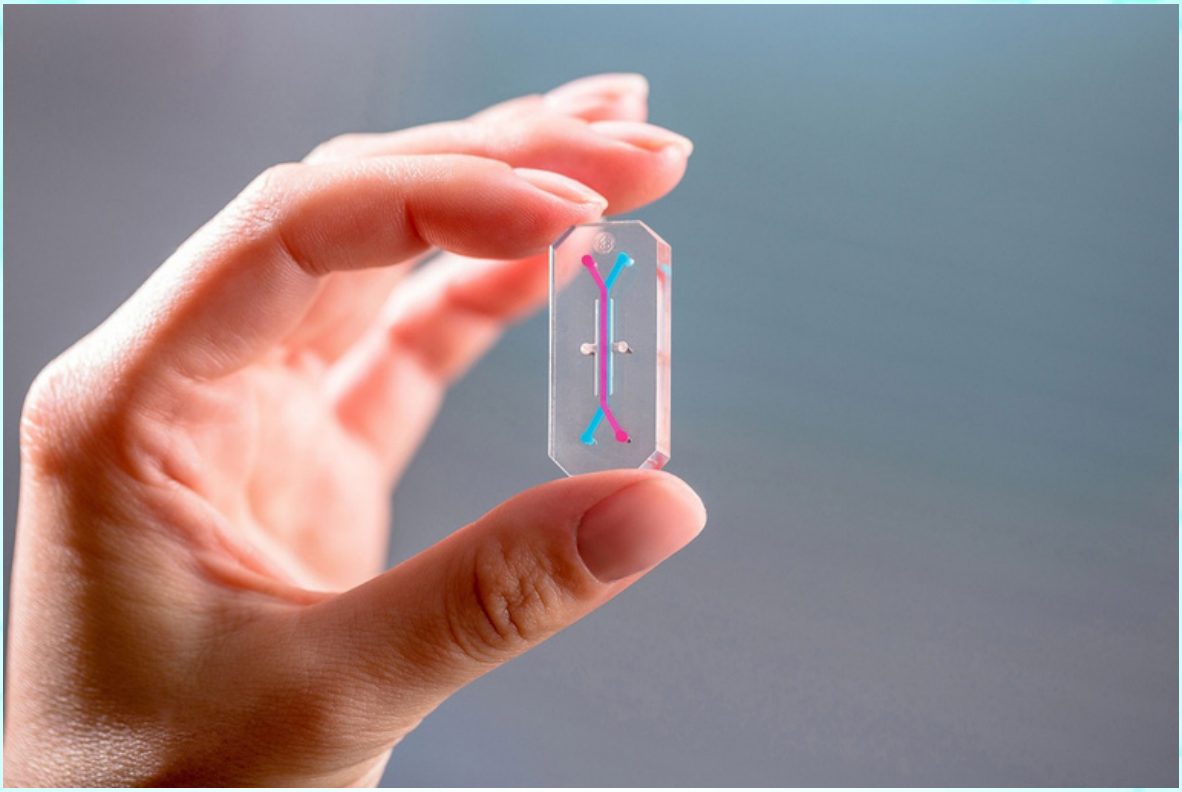


- Organ-on-a-Chip, a cutting-edge technology that can emulate the physiological environment and functionality of human organs on a chip for disease modeling and drug testing, shows great potential in revolutionizing the drug development pipeline.
- The future development of personalized Organ-on-a-Chip and continuous integration of novel engineering tools (e.g. automation handling, 3D printing, and in situ multi-sensors) and biological concepts (e.g. patient-specific iPSCs and organoid) into Organ-on-a-Chip platform will unprecedentedly promote its biomedical applications and bridge the gap between animal studies and clinical trials for the pharmaceutical industry.

- **WORLDWIDE STARTUPS : ORGAN- ON A- CHIP**

Company	Found Year	University Spin-off	Scientific Founders	Major Products	Region
Alveolix	2015	University of Bern	Olivier Guenat	Lung-on-chip	Switzerland
MesoBioTech	2016	N/A	Yong Chen	Microfluidics Lung chip	France
BiomimX	2017	The Polytechnic University of Milan	Alberto Redaelli	Heart-on-chip	Italy
BI/OND	2017	Delft University of Technology	Cinzia Silvestri	Organoids cultivation, Tissue-tissue interface	The Netherland
Jiksak Bioengineering	2017	N/A	Jiro Kawada Keita Shibuya Norihiro Yumoto Shinji Tokunaga	Nerve Organoids	Japan
DAXIANG	2018	N/A	Yu Zhou	Liver chip, cancer chip	China
Aracari Bio	2019	University of California, Irvine	G. Wesley Hatfield Christopher C.W. Hughes Steven C. George Abraham P. Lee	Vascularized micro-organ chip	United States
REVIVO Biosystems	2019	Agency for Science, Technology	Massimo Alberti	Microfluidic Skin-on-a-Chip	Singapore

• Future Prospects:

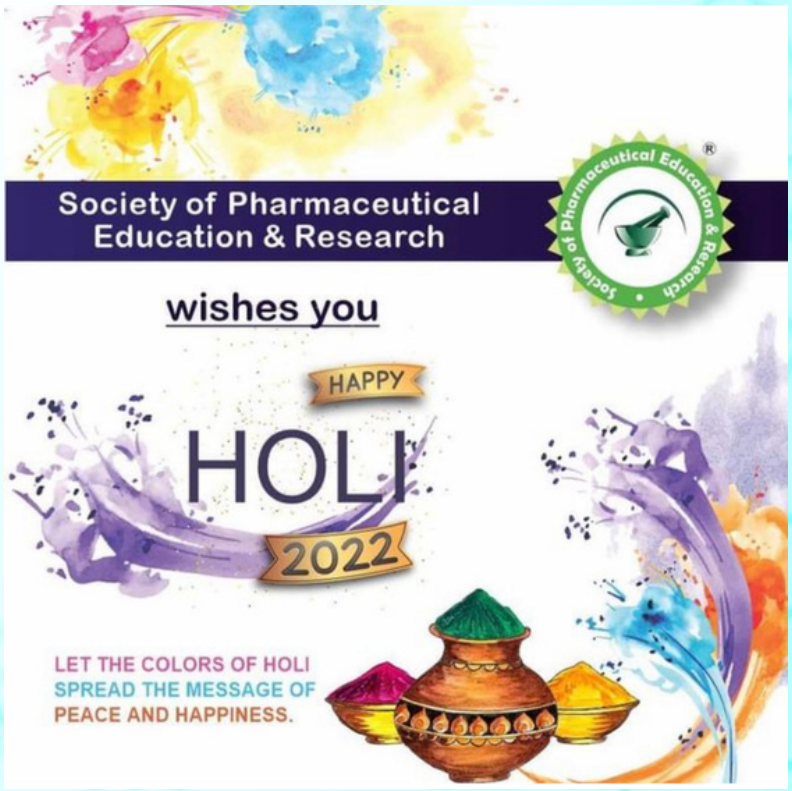


- The future Organ-on-a-Chip platforms will be able to demonstrate a physiologically relevant as well as spatiotemporally responsive microenvironment to solve the biological problems of interest.

- The future Organ-on-a-Chip platforms necessitate improvement as well as standardization of the product, its process of manufacturing with the categorization of the system designs, configurable elements, interfaces. Currently, most of the organ-on-a-Chip devices have been manually fabricated with PDMS in labs.

- The future Organ-on-a-Chip platform can be developed based on patient-derived materials, for instance- patient tissue decellularized extraneous material, as well as other biological materials. In personalized medicine, the selection of patients and their stratification biomarkers will be critical factors required for successful drug development.

SPER HIGHLIGHTS



JOIN SPER TODAY

- Join SPER to stay in connection with the recent happenings in the world of Pharma through our seminars, conferences, workshops, and publications. enjoy the exclusive member benefits - and shape your career in a new direction with great heights.
- SPER welcomes your contribution and participation in SPER events and activities and encourages you to access all of our exclusive member benefits and services.

CONNECT MORE

- Platform to get associated with a wide network of scholars and academicians interested in the growth of the pharmacy profession.
- Travel grant for students and young scientists to attend scientific international seminars and conferences

BENEFITS TO JOIN

- Information activities inside and outside the country through our updated website
- To get eligible for a number of awards as given by SPER
- Special discount (per article) in the Article Processing Charges (APC) for the Life Members of the SPER.
- Highly reduced registration fees at seminars, symposia, conferences, lectures, and exhibitions of the SPER

REFERENCES

- Socinski MA, Curigliano G, Jacobs I, Gumbiner B, MacDonald J, Thomas D. Clinical considerations for the development of biosimilars in oncology. MAbs. 2015;7:286–293.
- Mellstedt H, Niederwieser D, Ludwig H. The challenge of biosimilars. Ann Oncol. 2008;19:411–419.
- Kanters TA, Stevanovic J, Huys I, Vulto AG, Simoens S. Adoption of Biosimilar Infliximab for Rheumatoid Arthritis, Ankylosing Spondylitis, and Inflammatory Bowel Diseases in the EU5: A Budget Impact Analysis Using a Delphi Panel. Front Pharmacol. 2017;8:322
- Mody R, Goradia V, Gupta D. How similar are Biosimilars in India? A blind comparative study. Available from: http://www.pharmafocusasia.com/research_development/blind-comparative-study.html.06-03-2022
- United States Food and Drug Administration. Biological Product Definitions. Available from: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM581282.pdf.-06-03-2022
- Rezk MF, Pieper B. Treatment Outcomes with Biosimilars: Be Aware of the Nocebo Effect. Rheumatol Ther. 2017;4:209–218.
- http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe(06-03-2022)
- Leader B, Baca QJ, Golan DE. Protein therapeutics: a summary and pharmacological classification. Nat ReviewsDrug Discov. 2008;7: 21–39.
- Locatelli F, Roger S. Comparative testing and pharmacovigilance of biosimilars. Nephrol Dial Transplant. 2006;21(Suppl 5):13–6. [PubMed] [Google Scholar]
- Europa BIO. Spain Prevents Automatic Substitution Of Biological Medicines, Providing Clarity For Pharmacists And Patients. Available from: http://www.europabio.be/articles/PR_biosimilars_12-10-07FINAL.pdf.06-03-2022
- World Health Organization. Expert Committee on Biological Standardization. Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs). World Health Organization. October 23, 2009 (06-02-2022)
- https://www.chemistryworld.com/molecule-to-market/how-biologics-have-changed-the-rules-forpharma/3010301.article -06-03-2022
- Hincal F. An introduction to safety issues in biosimilars/follow-on
- biopharmaceuticals. J Med CBR Def. 2009;7:1–18.
- Leader B, Baca QJ, Golan DE. Protein therapeutics: a summary and
- pharmacological classification. NatReviews Drug Discov. 2008;7:
- 21–39.
- Biosimilars | FDA /www.fda.org/06-03-2022
- KYT Adhere. Digital Therapeutic Platform Optimizing Patient Engagement And Treatment Adherence. Available from: https://kytai/(06-03-2022)
- Somvanshi KK. Cipla may raise bar with digital therapeutics push [monograph on the internet] The Economic Times. Available from: https://economictimesindiatimescom/industry/healthcare/biotech/pharmaceuticals/cipla-may-raise-bar-with-digital-therapeutics-push/articleshow/71752197cmsfrom=mdr .(06-03-2022)
- Sepah SC, Jiang L, Peters AL. Long-term outcomes of a Web-based diabetes prevention program: 2-year results of a single-arm longitudinal study. J Med Internet Res. 2015 Apr 10;17(4):e92. doi: 10.2196/jmir.4052. PMID: 25863515; PMCID: PMC4409647.
- Whitesides GM. The origins and the future of microfluidics. Nature. 2006;442:368 73. https://doi.org/10.1038/nature05058.
- Sosa-Hernández JE, Villalba-Rodríguez AM, Romero-Castillo KD, Aguilar-Aguila-Isaías MA, García-Reyes IE, Hernández-Antonio A, Ahmed I, Sharma A, Parra-Saldívar R, Iqbal HMN. Organs-on-a-chip module: a review from the development and applications perspective. Micromachines (Basel). 2018. https://doi.org/10.3390/mi9100536.
- Katt ME, Placone AL, Wong AD, Xu ZS, Searson PC. In Vitro Tumor Models: Advantages, Disadvantages, Variables, and Selecting the Right Platform. Front Bioeng Biotechnol. 2016 Feb 12;4:12. doi: 10.3389/fbioe.2016.00012. PMID: 26904541; PMCID: PMC4751256.
- Allwardt, Vanessa & Ainscough, Alex & Viswanathan, Priyalakshmi & Sherrod, Stacy & Mclean, John & Haddrick, Malcolm & Pensabene, Virginia. (2020). Translational Roadmap for the Organs-on-a-Chip Industry toward Broad Adoption. Bioengineering (Basel, Switzerland). 7. 10.3390/bioengineering7030112.
- https://faunalytics.org/organ-on-a-chip-current-status-future-potential/(06-03-2022)

- DTA. Digital therapeutics alliance [homepage on the Internet] 2017. Available from: https://wwwdtxallianceorg/
- Goldsack J, Coder M, Fitzgerald C, Navar-Mattingly N, Coravos A, Atreja A. HealthXL Digital health, digital medicine, digital therapeutics (DTx): What's the difference [monograph on the interent] HealthXLcom. Available from: https://wwwhealthxlcom/blog/digital-health-digital-medicine-digital-therapeutics-dtx-whats-the-difference.
- https://dtxalliance.org/understanding-dtx/ (06-03-2022)
- Shi Y, Hu FB. The global implications of diabetes and cancer. Lancet. 2014 Jun 07;383(9933):1947–1948. doi: 10.1016/S0140-6736(14)60886-2. -
- NCD Risk Factor Collaboration Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet. 2016 Apr 09;387(10027):1513–1530. doi: 10.1016/S0140-6736(16)00618-8.
- American Diabetes Association Economic costs of diabetes in the U.S. in 2012. Diabetes Care. 2013 Apr;36(4):1033–1046. doi: 10.2337/dc12-2625.
- Centers for Disease Control and Prevention National diabetes statistics report, 2017. 2017. [2018-01-30]. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-stat... <ext-link xmlns:xlink="http://www.w3.org/1999/xlink" ext-link-type="uri" xlink:href="6wrxpE6QX"/>.
- Shahraz S, Pittas AG, Saadati M, Thomas CP, Lundquist CM, Kent DM. Change in testing, awareness of hemoglobin A1c result, and glycemic control in US adults, 2007-2014. JAMA. 2017 Dec 14;318(18):1825–1827. doi: 10.1001/jama.2017.11927.
- Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. 2017.
- ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018 May 15;71(19):e127-e248. doi: 10.1016/j.jacc.2017.11.006. Epub 2017 Nov 13. Erratum in: J Am Coll Cardiol. 2018 May 15;71(19):2275-2279. PMID: 29146535.
- Chen J, Abbod M, Shieh JS. Pain and stress detection using wearable sensors and devices-a review. Sensors (Basel) 2021;21:1030. doi: 10.3390/s21041030.
- van Hecke O, Torrance N, Smith BH. Chronic pain epidemiology - where do lifestyle factors fit in? Br J Pain. 2013 Nov;7(4):209-17. doi: 10.1177/2049463713493264. PMID: 26516524; PMCID: PMC4590163.
- Dang A, Arora D, Rane P. Role of digital therapeutics and the changing future of healthcare. J Family Med Prim Care. 2020 May 31;9(5):2207-2213. doi: 10.4103/jfmpc.jfmpc_105_20. PMID: 32754475; PMCID: PMC7380804.
- Sverdlov O, van Dam J, Hannesdottir K, Thornton-Wells T. Digital Therapeutics: An Integral Component of Digital Innovation in Drug Development. Clin Pharmacol Ther. 2018 Jul;104(1):72-80. doi: 10.1002/cpt.1036. Epub 2018 Feb 23. PMID: 29377057.
- Wu, Q., Liu, J., Wang, X. et al. Organ-on-a-chip: recent breakthroughs and future prospects. BioMed Eng OnLine 19, 9 (2020). https://doi.org/10.1186/s12938-020-0752-0
- Ma C, Peng Y, Li H, Chen W. Organ-on-a-Chip: A New Paradigm for Drug Development. Trends Pharmacol Sci. 2021 Feb;42(2):119-133. doi: 10.1016/j.tips.2020.11.009. Epub 2020 Dec 16. PMID: 33341248; PMCID: PMC7990030.
- Whitesides GM. The origins and the future of microfluidics. Nature. 2006;442:368 73. https://doi.org/10.1038/nature05058.
- Sosa-Hernández JE, Villalba-Rodríguez AM, Romero-Castillo KD, Aguilar-Aguila-Isaías MA, García-Reyes IE, Hernández-Antonio A, Ahmed I, Sharma A, Parra-Saldívar R, Iqbal HMN. Organs-on-a-chip module: a review from the development and applications perspective. Micromachines (Basel). 2018. https://doi.org/10.3390/mi9100536.