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Review Article

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Advances In Therapeutic Use of Microfluidics (Body on A Chip): A Review

Kulvinder Kochar Kaur[1]*, Gautam Allahbadia[2] and Mandeep Singh[3]

[1*]*Kulvinder Kaur Centre for Human Reproduction, India.*

[2]*Rotunda-A Centre for Human Reproduction, India.*

3Consultant Neurologist, Swami Satyanand Hospital, India.

***Corresponding Author**
Kulvinder Kochar Kaur, Kulvinder Kaur Centre for Human Reproduction, India.

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Abstract

Microfluidic technology with the advancement in biosensor technologyhas reached the arena of hospital set up leading to improvement in diagnostic as well as therapeutic fields with respect to various analytes,drug metabolites,delivery of drugs.Further enhancement has resulted in developments of cellular constructs right from tissues and various organs in the form of ''heart on a chip",or any organ on a chip" which involves any system of the body be it CVS,respiratory system,nervous,excretory ,digestive,skin or reproductive system both mimicking the normal physiology as well as pathologies which makes it easier to use it in the field oftreating any diseases as well as treating various cancers and testing the side effects of any drugs before delivering with cutting the cost on animal studies,since these BioMEMS have started becoming cheaper utilizing nano litres of the reagent and capacity to carry out umpteen tests in smaller volumes of samples and reagents.This review basically goes into the detail of organ on chipor biological /biomedical microelectrico-mechanical systems(BioMEMS)in medicinewith respect to different tissue engineering projects be it tissue transplantation or discovering newer drugs for treating cancer.

Keywords: Microfluidics; Organ on A Chip; Biomems; Hearton A Chip; Drug Delivery; Tissue Engineering; Pdms; Bionic Pancreas.

1. Introduction

Tissue engineering (TE) knowledge is being used in development of models, which are microengineered in human tissues and organs, getting verified as alternatives to animal modelsin finding the biological mechanisms which underlie morphogenetic and pathogenetic processes along with drug screening platforms [1-3]. Thus, this is a third dimension of TE to in vitro cell cultureswhich mimic the complex native tissues in a definitely better way, giving access to full human model.

Major advances in the field are integrating TE, with microelectronic, microfabricationand microfluidics. One has been using electronic devices for TE research. Biosensors used earlier for sensing biomolecules like proteins, peptides enzymes and DNA, are proposedin the field of tissue engineering for monitoring behavior of cells on a miniscale, having high sensitivity along with resolution with the benefit of lowering cost [4- 14]. Once the cellular analytes are found, electrical activity, physical along with chemical signals are transmitted by the cells and biosensors can give insights into cellular activitieswith responsein real time. Hence microfluidics-based sensors having an alternate name lab on chipandBiological/ Biomedical Electromedical Systems (BoMEMS)are getting more popular.

These are devices where manipulation along with fluid analysis is done in channels havingμm size [15,16]. Thus, microfluidics has been used successfully in diagnosis, manipulation of cells, along with drug delivery [17- 20]. Not only that, the greater advancement allows for signal monitoring and actively responding and adapting to them. This review highlights research on microfluidic devices and their applications in TE with latest development towards body on a chip concept.

1.1. Microfuidics

This is the science,technology used for controlling as well as manipulation of liquids at a few μL scale.This advantage of reduced minute volumes,scalability,laminar flow giving a fluid dynamic,which one can predict and has a good resolution and sensitivity,which cuts on the analysis time and is cheaper.Besides medical diagnosis, microfluidic is getting applied in testing drugs of abuse, detection of pollution, to fight biowarfare, besides use in routine laboratory in conducting research [21- 37]. Since it has high throughput capability it increases the number of assays conducted in automated manner and integrate them in huge experimental pipelines, simulataneously cutting down the cost. Instead of 96 wellplates for drug screen Chen and Ismeglev have synthesized microfluidic preloaded cartridges having nanoliters

plugs of reagents, same technology may be used for biological and chemical assays associated with low cost and simplicity [38]. Also assays which require thermocycling could be sped with the use of microfluidics technology [reviewed in ref [39]. With less reagent getting consumed, fast heating /cooling, short term assays are some benefits of mini-PCR devices and hence very useful in molecular diagnosis of diseases along withgene expression analysis [40- 46].

Some problems met in routine research are secondary to sample manipulation, measured signals get destablizedbecause of interference while loading a sample to change a buffer in addition to the time-consuming experiments and mostly due to lack of process automation. These negative points are got over in microfluidics by integration along with automation of routine laboratory techniques by which time, resources get saved besides bettering the qualityand giving reproducible results.

Afully integrated microfluidic platform for carrying out largely efficient capillary electrophoresisand electro spray ionization mass spectrometry analysis was useful for proteomic application as shown by Mellors et al [47]. While microfluidic cartridge for DNA purification and genotyping was developed using routine laboratory instruments as integrative systems [48]. Simple technology for point of care diagnostics is the paper based microfluidic systems where addition of methods of lateral flow tests and paper microfluidic technology in which a thin sheet of porous material in the substrate of bioassays, using the benefit of the high internal surface area of the substrate, capillary action and absorptive capacity [49].

Cell culture protocolcan be standardized with use of microfluidics and used in fl uid setting up of biosensitive assay protocols on which one relies and are very sensitive. Cells require proper physiological conditions, like pH, temperature, CO2 for ensuring them to remain active viable and therefore they have to be constantly perfused with nutrients and oxygen in uniformity, taking caution in avoiding biofoulingeffects of nonspecific adsorption of biomolecules [50].

To regulate microfluidics valves, pumps, mixers and otherfunctional elements allow cell perfusion using media and assay reagents which were fresh. Automated liquid handling controlling switch and valves electronically and multiplexing capability and detectors for monitoring cellular stimuli help in developing a high through put screening format possible. Different laboratory activities of microfluidics can be got from reviews [51, 52].

1.2. BioMEMSand Organ on Chips

Bio MEMS are increasingly being used in TE, give right control of the cell environment in areas which are suitable for cell screening. They also help the engineering and study of minimal functional modulesof complex tissues [53]. Though there is overlap of definition this latterapproach is also known as Organ on Chip (OoC).

The feautures of BioMEMS are use of vitro models of CVS,respiratory system,CNS,GIT,endocrine and integumentary systems along with their pathologies.Generally these devices are got by soft lithographic processes with poly dimethyl siloxane(PDMS) and glass ,which represent common materials in making microfluidic channels ,which makes such devices compatible with live cell microscopy and high throughputscreening methodologies. Devices may also bestow porous membranes to divide various cell populations into compartments and biomatic coating with ECMcomponent e.g. fibronectin, collagen, or Matrigel to improve cell attachment .Biomaterial related issue in making BioMEMS is given by Berthier etal in detaill[54].

1.3. Cardiovascular System (CVS)

Rather than direct treatment of CVS pathologies, microfluidic strategies and or device are being appliedin the in vitro models, diagnosis, clinical studies and drug screening, with the aim of decreasing the intervention time and formulating therapies, which are more successful. Because of conduit like design, and the exact control over flow conditions including shear stress, and pulsatility; microfluidics is most likely to be used as reductionist models of CVS biology (e.gto mimic blood flowand predict injuries to blood vessels) than study heart related issue. Modern biomedical engineering is advanced as well as capable of duplicating the CVS complexity.

Microfluidic cardiac cell cultures are physiologically relevant in vitro models,which recreate mechanical loading conditions seen in both normal and pathological conditions and thus allow stimulation of cardiomyocytes haemodynamically by coupling along with function with fluid induced loading [55,56].e.g of a ‘’heart on a chip’was given by use of poly (N isopropyl acrylamide)[PIPA Am)and PDMS construct, an anisotropic rat ventricular tissue and to measure contractility,action potential propagation,epinephrine dose responseand cytoskeleton architecture in a mid to high throughput system allowing realtime data collection[55].

Same group gave evidence that one can develop on chip, the negative remodeling of failing myocardium by applying cyclical mechanical overload [57]. It combined with cells/ biopsies harvested from patients, these models could be used as tools for drug screeningin individualized medicine. Main concern of microfluidic system for cardiovascular testing is the peculiar growth, attitude ofthecariomyocyte, which require special conditions to adhere and to survivewhile preserving their uniquecontractile phenotype. Finding the most appropriate and representative source of contractile cells is still a quest.

Once the vascular components of the CVS are taken into account, reproducing the complexityof system gives major challenge. Various groups have interest in development of microfluidic devices where angiogenesis [58,59]. artery structure and network, vascular endothelial function, growth and remodeling get studied. For more directed to vascular pathologies different groups focused in highlighting vasooclusive processes and thrombosis [60- 64].

evaluate hypertensive vessels or studying long term contractility [65, 66].

Various blood pathologiesare caused by the decrease of RBC deformability impeding the transit of these vessels through the microvasculatures where they play a major role in the oxygenization of tisues.Hence a common indicator of haemorheological dysfunction is the measure of RBC function deformability or dynamic analysisof blood flow.Biophysical properties including RBC aggregation ,deformability,viscosity,velocity profile and pressure of blood flows have been measured,in systems which were developed by Yeom, Guo,Tomailuolo along with Zhen and use effects of hemorheological features on the hemodynamic characteristics of capillary blood vessels [67-72].

1.4. Respiratory System

Commonly respiratory diseases have an effect on airways, lung tissue structure,circulation in the lung or a sum of all three.With the good minute controlin fluidic parameters with tissue interface ,modeling,microfluidic platforms are finding good applications to study respiratory system pathophysiology.Initial studies showed biometric system which reproduces the alveolar capillary interface of human lung or an alternative to animal and clinical studies for drug screening and toxicology applications .Subsequently vairious biometric models BioMEM or microfluidic based devices ,developed with purpose of highlighting and modeling important issue in lung development ,differentiation,homeostasis and disease[73]. Differentiation of lung stem/progenitor cells was studied with the angle that in long term lung tissue engineering applications could be developed [74,75]. Firstly, alveoli like structures were developed by seeding gelatin isolated mouse pulmonary stem/progenitor cells in a gelatin/microbubble backbone which was compatible by utilizing a2 channel fluid jacket microfluidic device [74]. Second approach was making microfludic, magnetic activated cellsorting systemin the isolation of mouse lung multipotent stem cells for further characterization [75]. There are groups trying to develop models which are just like lung barriers along with combination with cells from patients which is thought to work as drug screening platformsfor selecting drugs for therapeutic use in pulmonary diseases [76,77]. To sudy pathological onset of malignant conversion of bronchial epithelium due to tobacco, protein induced lung inflammation, chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis, bronchial systems are being producedto enhance our understanding of the molecular processes [78-81].

Also, microfluidic can be used for manufacture of implantable respiratory assist devices with a potential for clinincal application. A small scale microfluidic artificial lung and an implantable ambulatory lung assistance device was developed by Kniazva and Hogananbased on stacked microchannel networks, ultrathin gas exchange membraneswith an idea of being useful in therapeutic arena [82-85].

Though microfluidic artificial lung is still under development, various minidevices are now quite near \ use clinically. A portabe microfluidic device which had the ability to nebulize drugs into a fine aerosol for deep lung deposition viainhalation with a negligible drug degradation, was shown successfully in cases of epidermal growth factor receptor (EGFR) monoclonal antibodies [86]. Amini oxygenator device was manufactured by Rochow, which was made of stacked single microfluidic unitsand whose perfusion mimics an artificial placenta via umbilical blood vessels, which may support newborns having respiratory difficulty [80].

1.5. Nervous System

CNS pathologies arise secondary to ageing,brain and spinal cord injuries,genetic alterations etc.Although nervous system is very complex ,most developed techniquesof microfluidic technologiesare in vitro models,mimicking the nervous tissue-vascular interaction.Microfluidic platforms have been describedas ideal in vitro cerebrovascular model,partly because of automatized feautures which they possessalong with mini scale and secondly because oftheir ability to copy physiological dynamics ,physical properties and biological micro complexity[87]. Such devices can be appliedto model and study progression of neurodegenerative diseaseand screen drugs candidates towards individualized medicine solutions.

Blood brain barrier is thouht to be one of the major cause of aetiopathogenesisand progression of various neurological disorders like epilepsy,multiple sclerosis,parkinson's disease,and Alzheimer's disease.Hence a better understanding of the physiology,microenvironment,cell-cell interactions at the BBB level can give a hint regarding brain disorders or help in designing and testing efficient drug candidates.Booth upgraded the static(transwell)in invitro model of blood brain barrier(BBB) to a dynamic one and used it to analyze neuroactive drugs, thus making a model ne urons migratewhich was versatile to predict BBB clearance of pharmaceuticals [88, 89]. Understanding the mechanisms regarding function of formation of neuronal network scan be improved by the in vitro microfluidics based model in normal physiological conditions. One can thus reproduce synaptic competition, authentication of cell lines, study how neurons migrate in embryonic brain explants, axonal guidanceduring braindevelopment, along with myelination [90- 94].

Use of microfluidic devices allows to expose to multiple compounds at once in sequence, thus improving the exisent models towards an individualized medicine approach as a guided therapeutic decision making [95- 97]. Possibility of utilizing microf luids regarding highthroughput mapping of brain wide activityin awakeand drug responsive vertebrateseg zebrafish is there [98]. Understanding the basic physiologicalchangeswhich occur during the onset of neurodegenarativediseases, microfluidic systems were engineered tomodel synaptic connectivity between mixed hippocampal coculture, for reconstructing neuronal networks and test β-amyloidtoxicity, as well as to follow activationof developmentalbrain disorders [99- 102]. Structural and functional deficitspredict an easy occurrence of neuro degenerative diseases

at the axonal level. Hence various platforms have been fabricated to underline mechanisms of axonal function impairment, axon polarization, axon toxicity deformation and to trace axonal transportat single vesiclelevel [103- 110].

1.6. Digestive and Excretory Systems

Diseases of the GIT like stomach and esophagus cancer, short bowel syndrome, fecal incontinenceand trauma affect GIT function, requirelooking for treatment options. To diagnose early Zilbamen, Sonkus brought out a method using optico electronic sensors for early gastric cancerdetection in saliva, an alternative noninvasive method to endoscopic biopsy and histopathological evaluation [111].

Problem with that is standard 2D culture systems cannot be reproduced, with chemical complexity and biofunctionality of the living tissues, microfluidics arose as alternative platform to develop strategies to settle GI T tissue regenerationand study organ physiological functionality. Structure and dynamic feauturesof BioMEMS, there is great interest in the use of these systems to study the intestinal absorption of drugs and their toxicity, e. g Kimura and colleagues developed an integrated microfluidic system endowing on chip''pumping and optical fiber detection systems. Performance of the choice was examined through long term culture and monitoring of polarized transport activity of Caco2 cells [112]. Similar drug transport model using microfluidic devices have been given by Mohlar et al and McAuliffe et al [113-114].

In vitromodels of the intestine using microfluidics systems are important tools for studying the gut function both under normal or diseased condition and to perform drug screening and toxicity assays. Kim et al made a humangut on chip'', which was composed of 2microfluidic channels with a flexible porous membrane coated with extracellular matrix lined by gut structure with it mechanical, absorptive transport and pathophysiological properties [115]. Kim and Ihgban showed that applying specific physiological mechanical cuesto the gut on a chip, one could produ ce Caco2 cells to undergo intestinal villi morphogenesis later [116].

Upgradation of this modeling was done by ma king platforms which can be adapted to produce various functional units of other organs [117]. Improvement in the intestinal epithelium on a chip''e.g., a 3 D shaped microporous polymeric membrane which ape the geometry of intestinal villi or by intestinal epithelium on achip'' getting reproduced with the use of a novel hydrogen microfabrica tion technique and showing a superior structuratual maturation [118, 119]. Same device was also used to study the kineticsof diffusion processesin the 3D villi backbone.

Much more complex structure was made by Ramdan etalusing microfluidic platforms named Nutrichip.The objective was to analyze the passage of nutrients through the GIT, which includedthe epithelial and immune cell components for pro and anti-inflammatory stimuli was monitored [119]. In digestion the liver's role is in filtering nutrients and digestion products. Also, liver plays an important role in the metabolism of xenobiotics and hence lots of articles were there in recent year for recreating liver specific functions through microengineered models, with [120-124].

Also, several articles explained use of microfluidics to develop hepatocyte cells cultures and were physiologically relevant, differentiation and coculture systems, along with design of platforms to investigate liver drug metabolism and toxicity, which are basic tools for addressing liver pathologies and give insight into molecular studies and-mechanisms, and similardrug-drugand organ-organ interactions-von Midwoud et al [125- 137]. (v)enzymes/hormones or blockade by tumours and gallstones=>malfunction of whole digestive system. Use of microfluidics has been done for stdying pancreatic cancer, culture pancreatic islets, monitor stimulus secretion factors and promote tissue specific cell differentiation [118, 138- 148]. Bionic pancreasdeveloped for type 1 diabetes mellitus, which uses continuous glucose monitoring along with subcutaneous deliveryof both rapid acting insulin and glucagonto lower/increase blood glucose levelsis a good example of use of microfluidic technology [149].

Kidneys are of importance for whole body homeostasisbecause of the important functions in processing digestion products, water balancealong with BP regulation. Hence newer strategies to treat the biggest problems involving kidneys is needed,of which chronic kidney diseaseresulting in end stage renal replacement therapyand eventual transplantation=>massive load on various health care systems.Leonard et al used very novel tools to improve end result of classical approaches, e.g membraneless dialysisstrategy was developed opening possibility to create wearableblood processing devices[115,150].Culture of kidney cells in tubular structureswhich ape the organ structure and function are developed by microfluidics.Also microfluidics can be used to model diseases ,metabolism studies,insight overkidney cell toxicityand renal clearance[151- 157].Renal excretion and metabolism are the actual subjects of preclinical safety studieswith goal of investigating drug pharmacokineticsin vivo like pathophysiological conditions. Hencedevices utilizing microfluidics can be of use in co-culturing different cell types Along with impact on the recreation of multiorgan system to studysystem interactions where kidneys and also liver can be incorporated [158].

1.7. Other Systems

Still in budding stagessome microfluidic platformslike for adrenal gland are being used to find corrticosteroid and catecholamines [59- 164]. With regards to fertility Huang et al used it to analyze and separate and quantify spermatozoids [165]. Tung et al showed that biophysical environment of female reproductive tract critically guides sperm migaration without helping the pathogens to migrate [166].

Kim etal used to quantify steroid hormoneslevels in tissues, and in human serum, which can be useful in fertility as well as in

osteoporosis studies [167, 168]. It has also been found to be of use in thyroid disease diagnosis [Shamsi and Medah et al [17, 169]. In hormone responsive cancers Lang et al explored breast cancer microenvironment activity using protein levels as a sensorto predict how cell signaling is related to growth of cancer cells [170]. While Kim et al studied how Studying tumor chemoinvasion processes are affected by chemical gradient, studying tumor cell migration behavior to understand the first steps of carcinoma metastasis [171].

There are also novel applications on the wearable sensors for continuous physiological signal monitoring. Non invasive biofluid namely sweat is under deep investigation e.g Rose et al along with Liu et al made sensor patches for sweat electrolyte monitoring and aiming at hydration control [172, 173]. Xu et al., described experimental and therapeutic approaches for soft microfluidic assemblies in sensors circuit radios for the skin [174]. Sonner et al., reviewed microfluidic models for eccrine sweat generation and flow, as a guded sweat based diagnostic development [175]. Other approaches to investigate the function and deficits for tiss ue-tissue integumentary system comprise the microfluidic platform developed to study the accumulation of molecules at the basal lamina interfaces and achieve efficient drugs and carriers' distribution through biological barriers [176]. Microfluidic application to models skin diseases and for skin tissue regeneration are still in an early stage. Still work regarding wound healing and cell migration, which showed that this technology may have potential to treat skin injuries [176- 179].

1.8. Future FunctIion- Body on a Chip

Number of new drugs approved /billion US$ spent on RD has been halved falling around 80fold in inflation terms. It is important to better the efficacy of preclinical trials to predict the tumor / drug selection to avoid costly failures. W ith the microfluidic microengineered models of functional units of human organs. This approach provides the basis for preclinincal assay with predictive power [2]. These are extended to recapitulate the function of several organs on a single microfluidic platform with the final goal to mimic the body physiology. Hence BoC concept is gaining importanceas a suitable cell-drugand cell-cell response [180].

BoC devices are made up of microfluidic, into which several modules can be installed holding different cell types or engineered human organs [181]. Samples are interconnectedin a hierarchic and physiologically relevant fashion, thus allowing the functional modeling and monitoring of the circulatory, endocrine, digestive, immune, lymphatic, nervous, respiratory and urinary systems as an advanced human in vitro model.

Because BoC apes' physiology and important aspects of metabolism they allow to

• predict in high accuracy as well as comprehensive analysis of novel therapeutic candidates in preclinical stages, by a better estimation of efficiency along with response

• decrease and possible replacement of animals in preclinical drug development, therapy decreasing costs and time to market

• creating drug development tools which helpmodern medicine io be able to cope with rapid moving pandemicsor chemical warfareor bioterrorist attacks

• By monitoring metabolites be able study cell signaling, which get consumed, produced and exchangedbeteen different tissuesin physiological concentrationsin real time

• Following intercellular signalsand/or biochemical messagesto study embryology

• carry out experiments which can't be done in cell cultures e.g studying tissue-tissue interactionwhich occur because of the metabolite moving from the tissuesto some distance issue along withdynamic forces which mimic blood circulation

• cell-cell and cell-drug /biomaterial interaction which is efficacious along with trustworthy, by which the gap between in vivo and in vitro conditions gets smaller.

More use of microfuidics can be obtained if it is complemented with sensitive methods of analysis like mass spectrometry and sensors, and hence one can do profiling of metabolites along with molecularly characterizing the chip-based systems. Since the chip channels are transparent it is possible to monitor cell response along with performing cell tracking through time lapse live –cell imaging.

There are two types of approaches for BoC which complement each otheri) the bottom-up approach which start with specifying each organ in detailand then move with the design of coupled systeme. g-heart-lung and intestine-liver and adding organs to further created models which are more complex.2) Top-down models which conversely take into consideration the abstract system level architecture of an organism and then break the system down, into functionality of compositional organ systems.

One can also study inflammatory process by adding cytokines/ living immune cells to the systems [182, 183]. BoC devices along with biopsy samples or cells from individual patient can be of great help for developing medicine which can individualize treatment for predicting how a patient may react to a particular pharmacological drug, even before deliver it and hence decreasing risks [184].

1.9. Usefulness of BoC's

Different BoC's are getting manufactured e.g.BoC stimulationwith GIT and liver tissue was prepared by coculturing Caco2 enterocytes,TH29-MTXmucin most of platforms producing cell lines and Hep/C3a hepatocytes in a microfluidic device .The results proposed thatingestion of carboxylated polystyrene nano particles have the capability of causing liver injury,thus showing how important BoC's devices are in vito multicellular models for evaluating nano particles interactions with human tissues[180]. Vunjak –Novakokovic et aldeveloped the HeLi Va platform, an integration of heart-liver-vascularsystem derived from a single line of human pluripotent stem cells and thus allowed human physiology to be representedfunctionally along with realtime biological

readoutsand was compatible with high throughputanalysis [185]. First pass intestine and liver metabolic s of paracetamol coupled with mathematical modeling as a means to evaluate absorption, distribution, metabolism and excretion [ADME] processes in tissueswas given by Prot et al [186]. Thus, this was the first step in an integrated strategy which combined in silicoand in vitro methods based on microfluidic for evaluating drug ADME processes is the overall approach [186]. One year later 4 organ –chip for interconnectedlong term coculture of human intestine, liver, skin and kidney equivalents were introduced [187]. In this system almost near to physiological fluid to tissue communication. between the different cell and tissue types, ratiosand establish reproducible homeostasis in cocultures, sustained over atleast 28days [188]. This system is hence a powerful, important tool which can carry out in vitro microfluidic ADME profiling and repeated dose system toxicity testing of drug candidates [189]. A 96 wellformal based microfluidic platform was prepared to interconnect several multicellular 3D spheroids which enabled parallelized culturing and testing of spherical microtissues of different cell typesin the standard incubaor [190]. With this kind of device tissue-tissue interactions can be studied in presence of pharmalogical component. Swiss startup, its manufacturer gives 3 years time for the commercial In Sphero multitissue Adevice to get constructed.

Connecting different chips for increasing physiological relevanceof the in vitro system effects are being made in recreating whole human bodyby bridging the fluidics of multiple chips ,so that the physiological pharmacokinetics of the drug of interest can be studied in a very complex representative in vitro system.In a first approach this pharmacokinetics pharmacodynamic platform as tested using three cell lineswhich represented liver,tumor and bone marrow, but can also be extrapolated for more organs to predict mammalian responseto drugs and chemicals [191, 192].

Having a similar objective Ingler DE made an organ on chip which replicates key functional units of living organs to make integrated human organ level pathophysiologyin vitro [117,193]. The other purpose would be combining multiple organs as possible close to a real human body.The development of ATHENA(Advanced Tissue Engineered Human Ectypal Network Analyzer) platform also known as Homo Minutus'',inwhich 4 interconnectedhuman organs constructs(liver,heart,lung and kidney)are interconnected in a highly miniaturizedplatform follows the same principle [194]. This Benchtop Human'' is a great promise as it has abilty to mimic the spatial and functional complexity of human organs=>to a more acquired way of screening new drugsfor potency and potential side effects than current methods [195].

1.10. Cancer and Boc

There is a search for newer cancer prevention and diagnostic tools and studying signals particular to cancermicroenvironment and which allow tumor cell growth and malignancy along with transvascular migration [196- 203]. There is awareness that tumorcell migration along with intravasation into capillaries is the initial event in metastasis of cancer. Different platforms have been made, with the objective to make out efficiently and harvest circulating tumor cancer cells (CTC's), along withclusters, and for chemosensitivityor chemokine assays. Various works report the development of microfluidic deviceforthe isolation of CTCs from lungs [196, 201, 204-206], pancreatic. [138, 139], breast [197, 205,208], ovarian [197,208], prostate [197,206,207]. colorectal [209], gastric [207], hepatic [210] and skin(melanoma) [207] cancer.

The expression of specific cell surface markerswas constructed by Huang et al [211]. Another 3D microfluidic chipwas made by Yang et alwith a concentration gradient of hepatocyte growth factor(HGF) to see the effect on Met/Pi3K/Aktactivation,a glucose regulatory protein expression and paclitaxelinduced A549 cell apoptosis, as to simulate the in vivo secretion of growth factor by cancer associated fibroblasts.Further Kao et al used direct current elastic fields in a microfluidic cell culture device obtaininig bothstable electric fieldsand concentration gradient [212- 213]. Trying to be closer to personalized medicine approach Ruppen et al allowed the possibitity of reproducing in part,the barrier formed by the tumour microenvironment to protect the tumor from drug exposureby testing the chemosensitivity of the patient lung cancer cell spheroidin a perfused microfluidic platform [214].Tumor extravasation and metastatic sitespecific have been investigated using 3D microfluidic platform [215, 216].Various systems allow for the capture of CTC's and clustersfrom blood samples for furtherdetailed analysisof biomarkers by flow cytometry technology and multiimaging [205, 199-201].Capturing these cells or clusters is ideal for detecting patients with metastatic cancerand RNA sequencing of cancer cells can detect regarding the presence of cell mutations and detect the tumor origin[214].

2. Shortcomings of Boc's&Conclusions

This is a compex biology to construct a meaningful model for studying the full properties of a whole system. Calculating the exact size of every organ along with its vascular conditions, perfusing organ units, withexact surface to volume ratioand getting it into the systems which models describing the states of healthand disease, are some of the challenges regarding bringing this BoC to clinical use [188, 192, 193].

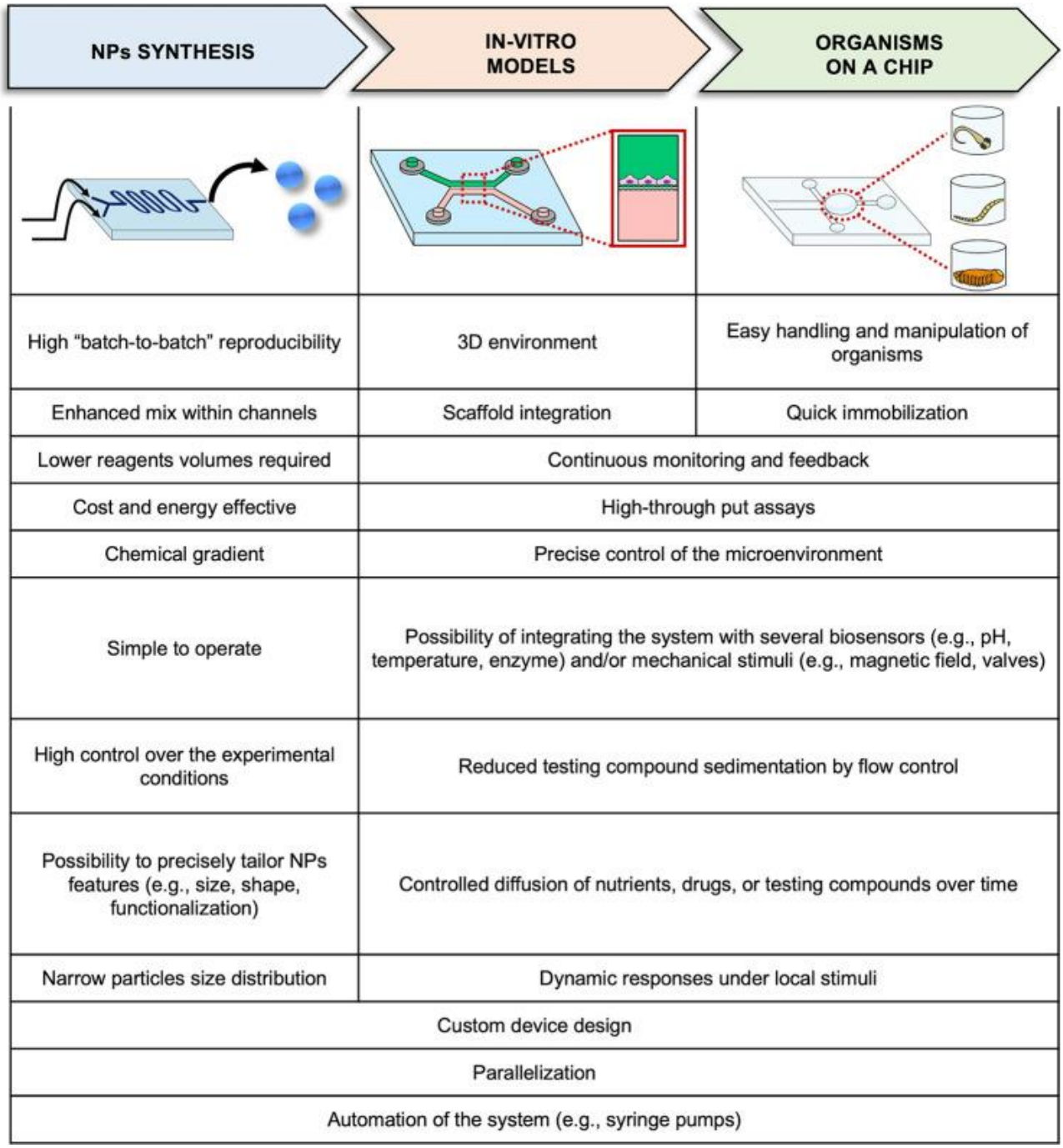
Lot of drawbacks are there from a more operational perspectivein view of their µ scale ,mainly related to the growth of such minute channels,formation of airbubbles in cell cuture channels and the hurdle of long term experiment[117].Other problem of BoC's is that its use on a daily basis,for which one needs to redesign it to become simpler,flexibleand userfriendy and it to be appled as benchtop analyzers.The effect of the polymers and fluid utilized in BoC's exert on cell behavior and in adsorption of metabolitesare still not well understood.Hence challenges researchers need to address is physiological(a universal blood surrogate)which enables the preservation of cellular phenotypeand provide an effective humoral communicationbetween the different cell and tissue types[188].

Inspite of these limitations to reach commercialization there are various devices already approved and/or are under approval by FDA e. g are Cell Search@ disease considered as the first FDA approved CTC diagnostic technologyfor clinical use and the only actionable test for finding CTCs in metastatic breast, prostate and colorectal cancer. It is being applied in preclinical studies [217]. With the high technology advances being observed year after year most platforms described here may be the futureones fit for FDA rules.

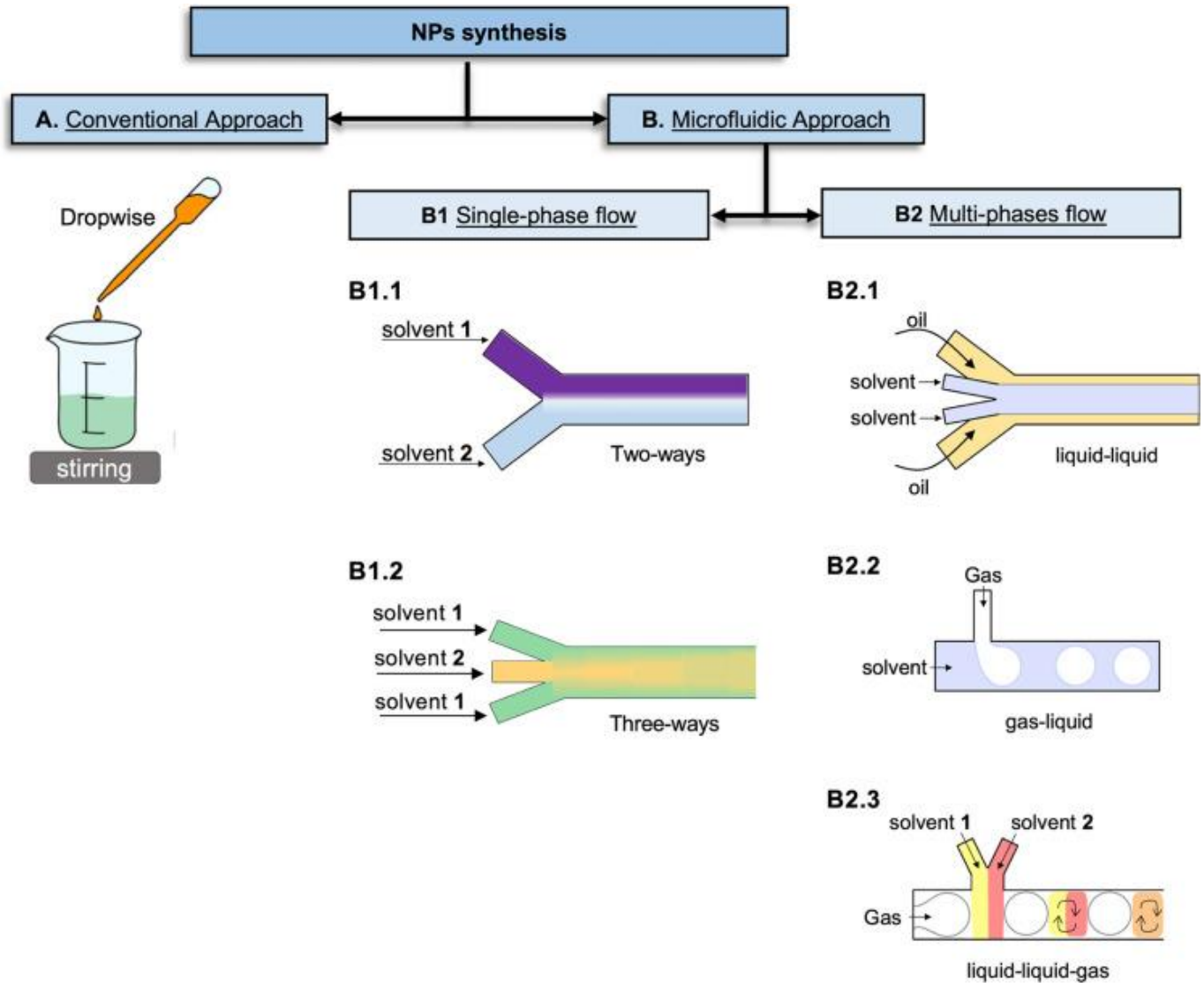
BoC's are a step forward with all drawbacks existent in the in vitro modelsand with the complexity found in animal models, BoC's play a role as a platform which allows identifying multiorgan toxicityand for decreased efficiency due to metabolic activity. BoC's have the capability of improving drug development processes significantly,and also better the knowledge in tissue-tissueand or tissue-biomaterials interactions,decreasing the gap between in vivo and in vitro conditions in TE applications along with diseasae progression studies.

Recent Updated

The utilization of nanoparticles (NPs) in nanomedicineholds great promise for the treatment of diseases for which canonical therapies present robust restrictions. Furthermore, NPs migh result in dramatic improvementof early diagnosis in addition to follow-up of numerous conditions, Nevertheless, regarding harnessing their total capacity, they need to be generated in addition to evaluated in germane models. Microfluidic systems possess the capacity of mimicking dynamic fluid flows, gradients, particularmicroenvironments, as well as and multiorgan complexes, yielding an efficacious along with economical strategy forboth NPs formation as well asimmoblization. Microfluidic technologies contribute to the development of NPs in case ofregulated situations, escalating batch-to-batch replication. Additionally in view of the versatility of microfluidic devices, vit is possible to generate andcustomize endless platforms for rapid and efficient in vitro and in vivo screening of NPs' performance. Indeed, Gimondi microfluidicdevices show great potential as advanced systems for small organism manipulation as well as immobilization. Gimondi etal.[219], reviewed first themain microfluidic platforms which aid in NPs regulateddevelopment., subsequently they detailed the maximum innovativemicrofluidic platforms which aid in simulating in vitro environments as well as give insights into organism-on-a-chip and theirattractive application for NPs screening. Lastly, they critically evaluated the present challenges in addition to probablefuture directions of microfluidic systems in NPs generation as well as screening the influence on the field of nanomedicine.

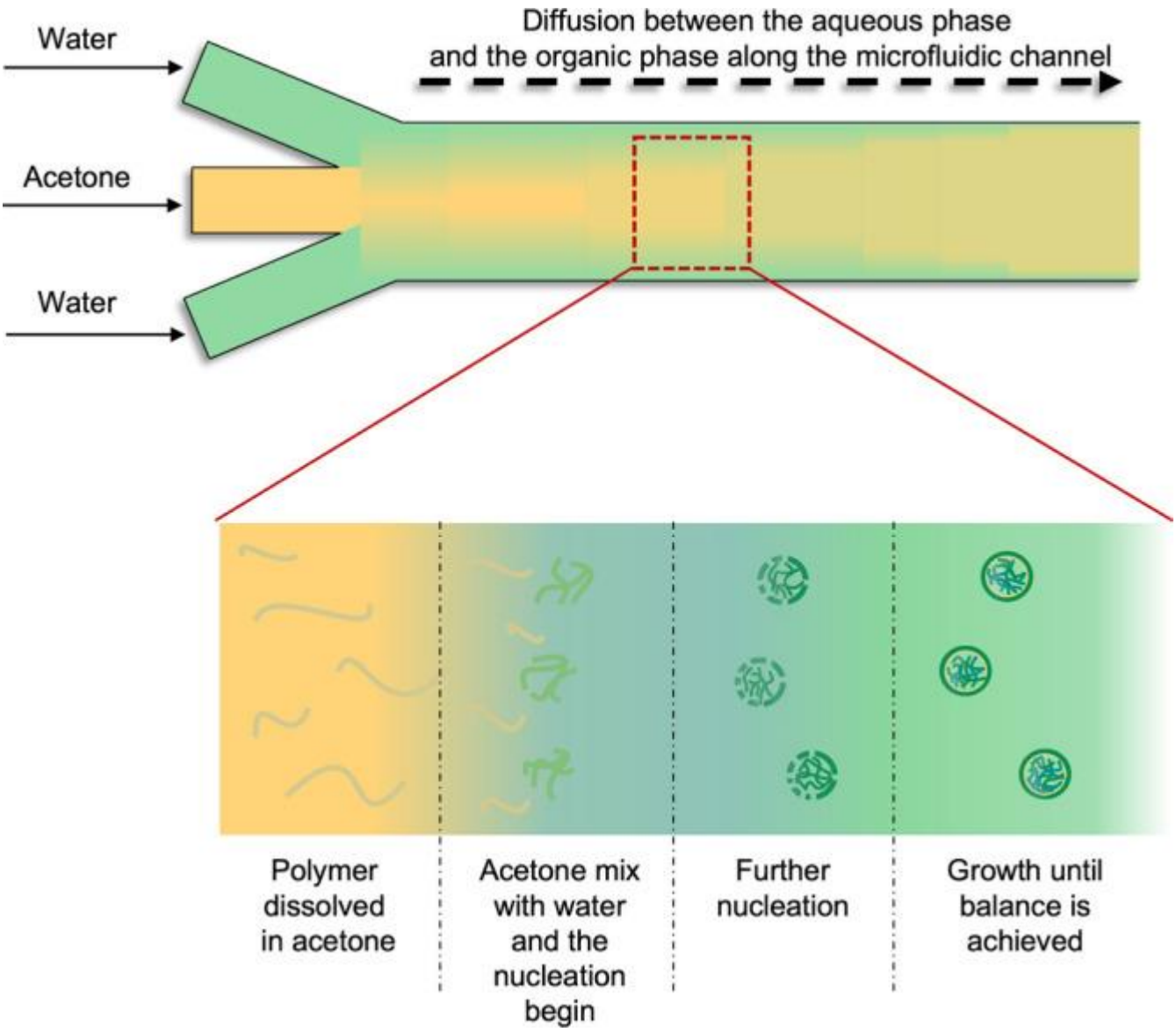


Legend for Figure 1:
courtesy ref no-219 Scheme illustrating the microfluidics application in NPs synthesis, in vitro models, and organism-on-a-chip and their advantages. To date, microfluidics technologies allowed improvement of the NP synthesis process and in vitro and in vivo screening through the manipulation of, respectively, 3D cell cultures and small organisms, such as Caenorhabditis elegans worms, Drosophila melanogaster, and Danio rerio larvae inside microfluidic devices.



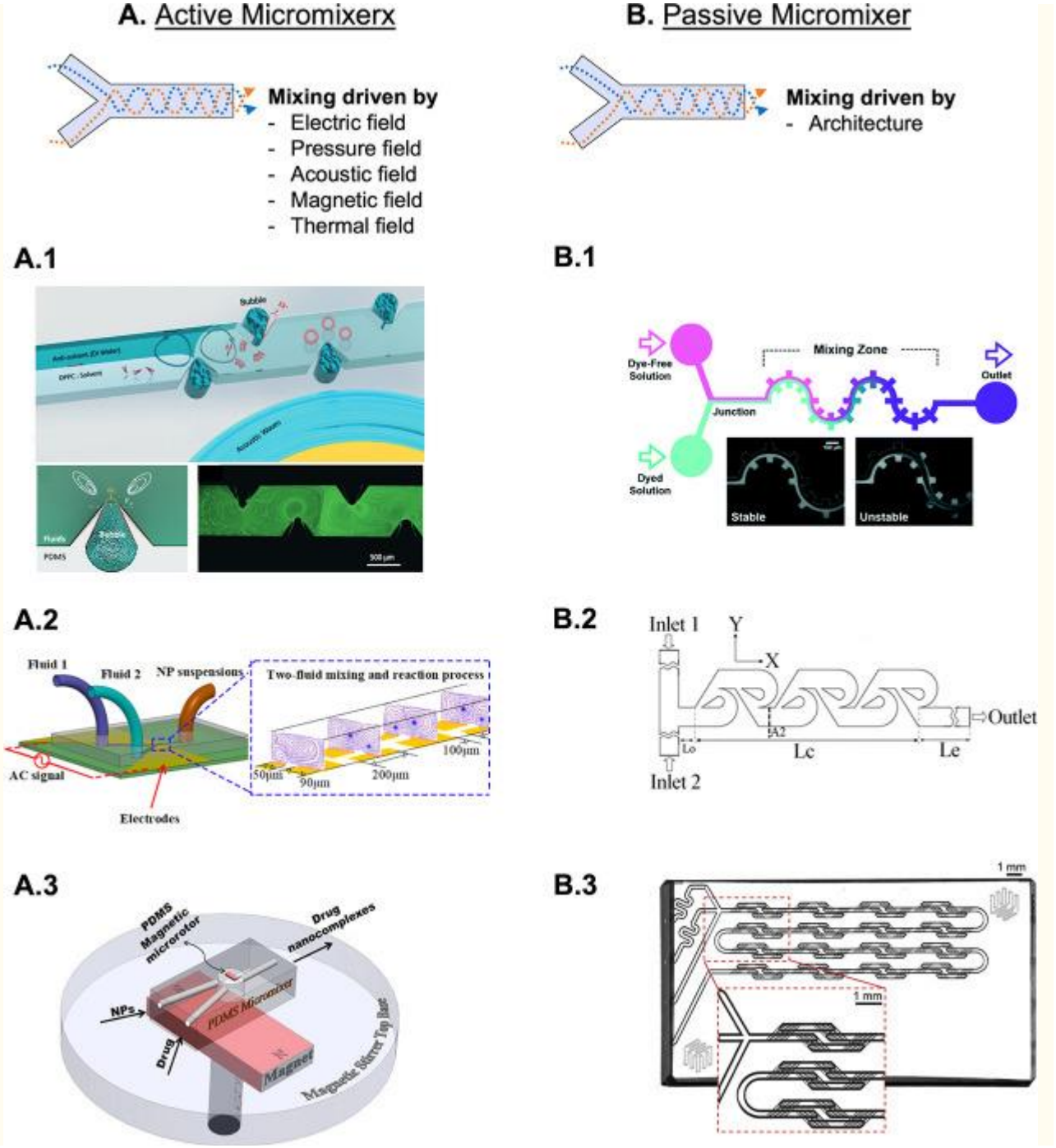
Legend for Figure 2:

courtesy ref no-219 Schematic representation of one of the most used conventional approaches for NP generation, the dropwise method (A). Microfluidic chips (B) with different designs can be employed for NP production based on the type of flow used, namely, single-phase flow (B1) with two- (B1.1) or three-way channels (B1.2), and multiphase flow systems (B2), such as the liquid–liquid (B2.1), the gas–liquid (B2.2), and the liquid–liquid-gas (B2.3).



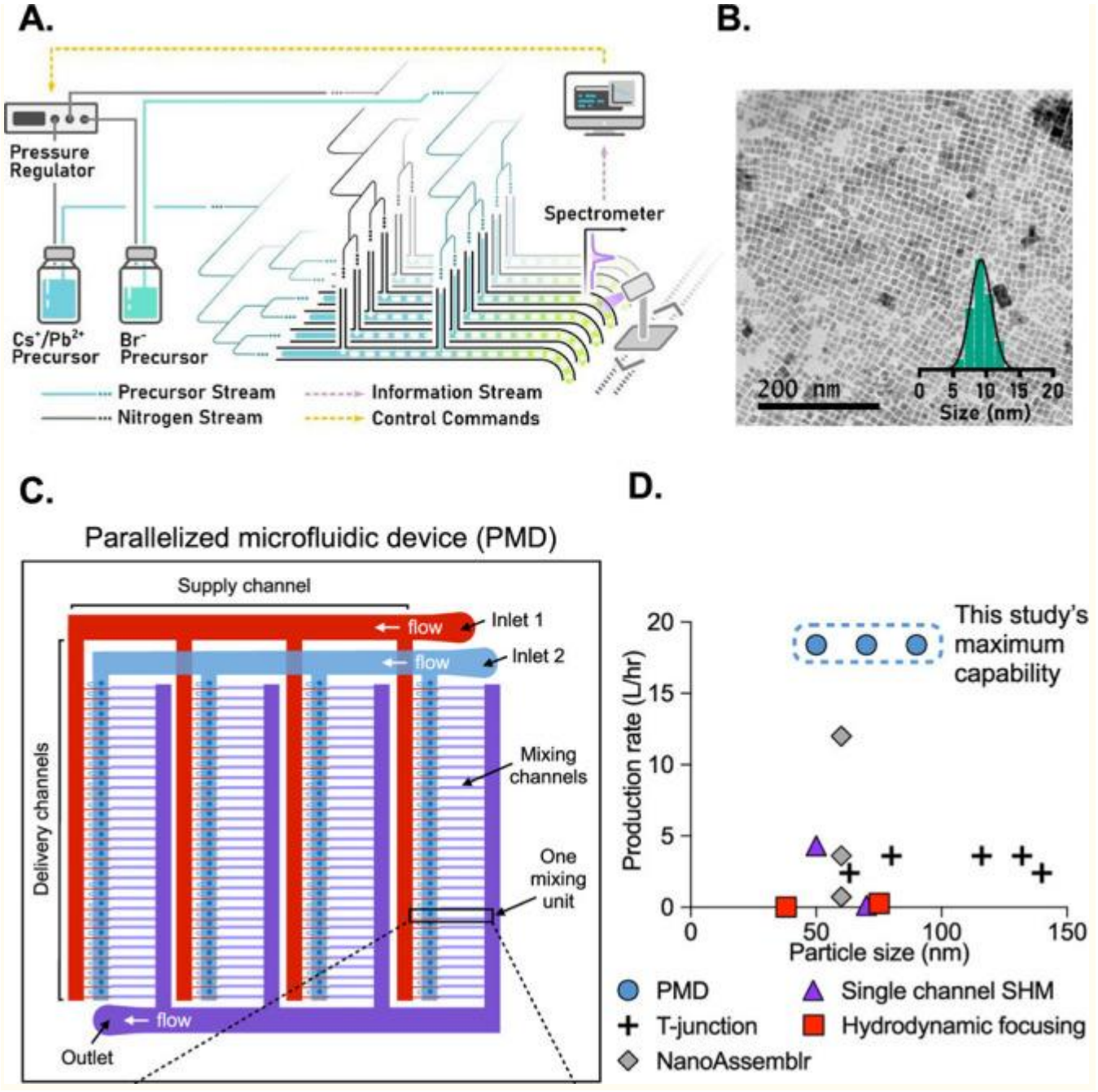
Legend for Figure 3:

courtesy ref no-219 Mixing process inside a linear microfluidic chip between two miscible solvents, such as water and acetone, occurs due to the diffusion of the acetone into the water, generating a homogeneous solution along the channel. For nanoprecipitation, a hydrophobic polymer soluble in an organic solvent (acetone) can precipitate due to its poor solubility in water. Consequently, as the diffusion progresses, the polymer chains collapse on themselves and aggregate (nucleation phase) into NPs. The rapid mix improves the reaction of nucleation and growth, until the balance is achieved and uniform NPs are generated.



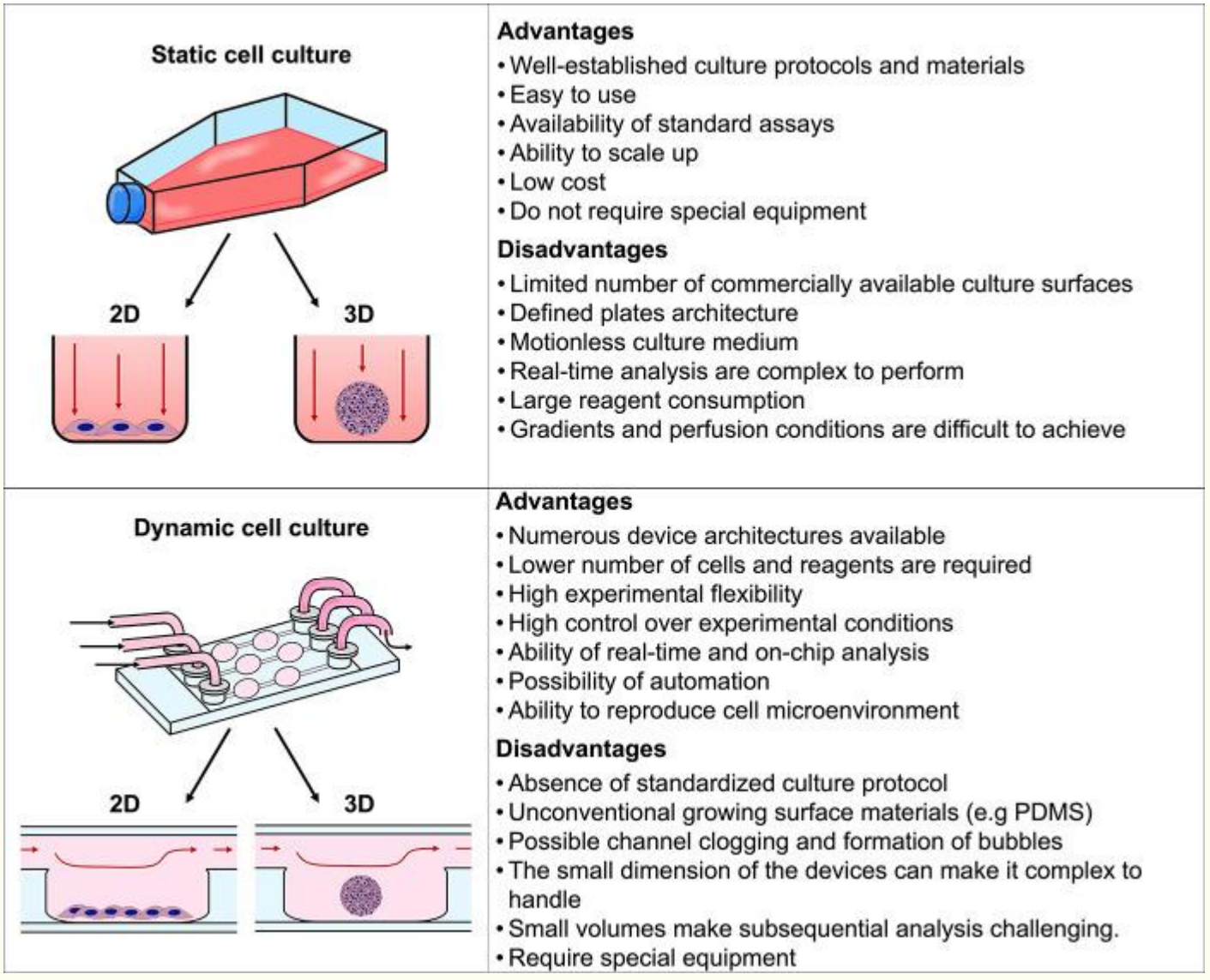
Legend for Figure 4:

Examples of active micromixers (A) where the mixing of the injected fluids is induced by acoustic waves (A.1 - Adapted with permission from ref (rev in ref 219). Copyright 2019 Royal Society of Chemistry), alternating current electrothermal field (A.2 - Adapted with permission from ref (rev in ref 219). Copyright 2020 American Chemical Society), or magnetic field (A.3 - Adapted with permission from ref (rev in ref 219). Copyright 2016 Elsevier). In the passive devices (B), the mix is achieved due to the architecture of the channels, such as the gear shape (B.1 - Reprinted with permission from ref (rev in ref 219). Copyright 2021 Royal Society of Chemistry), the tesla (B.2 - Reprinted with permission from ref (rev in ref 219). Copyright 2010 Elsevier), and the herringbone (B.3) micromixers.



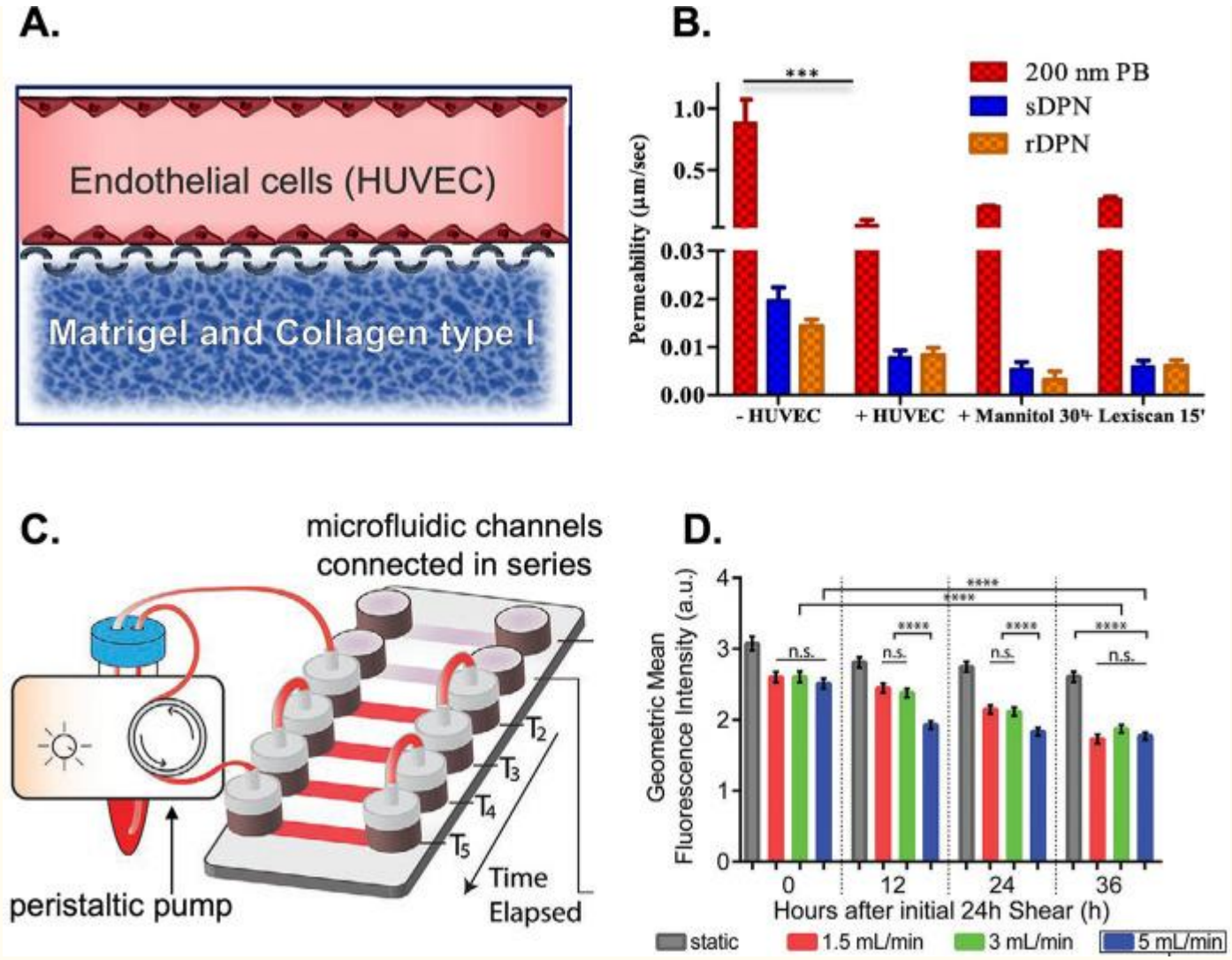
Legend for Figure 5:

Schematic representation of a 16-channel microfluidic reactor equipped with an integrated system for photoluminescence monitoring (A - Reprinted with permission from ref (rev in ref 219). Copyright 2020 Royal Society of Chemistry). The resulting quantum dots obtained from this reactor exhibited a consistent average size of □10 nm (B - Reprinted with permission from ref (rev in ref 219). Copyright 2020 Royal Society of Chemistry). The parallelized microfluidic device incorporates an array of 128 mixing channels (C - Reprinted with permission from ref (rev in ref 219). Copyright 2021 American Chemical Society). The production rate of this parallelized microfluidic device (PMD) was compared to alternative approaches, with a focus on the total volumetric production rate and the corresponding size of lipid NPs (D - Reprinted with permission from ref (rev in ref 219). Copyright 2021 American Chemical Society).



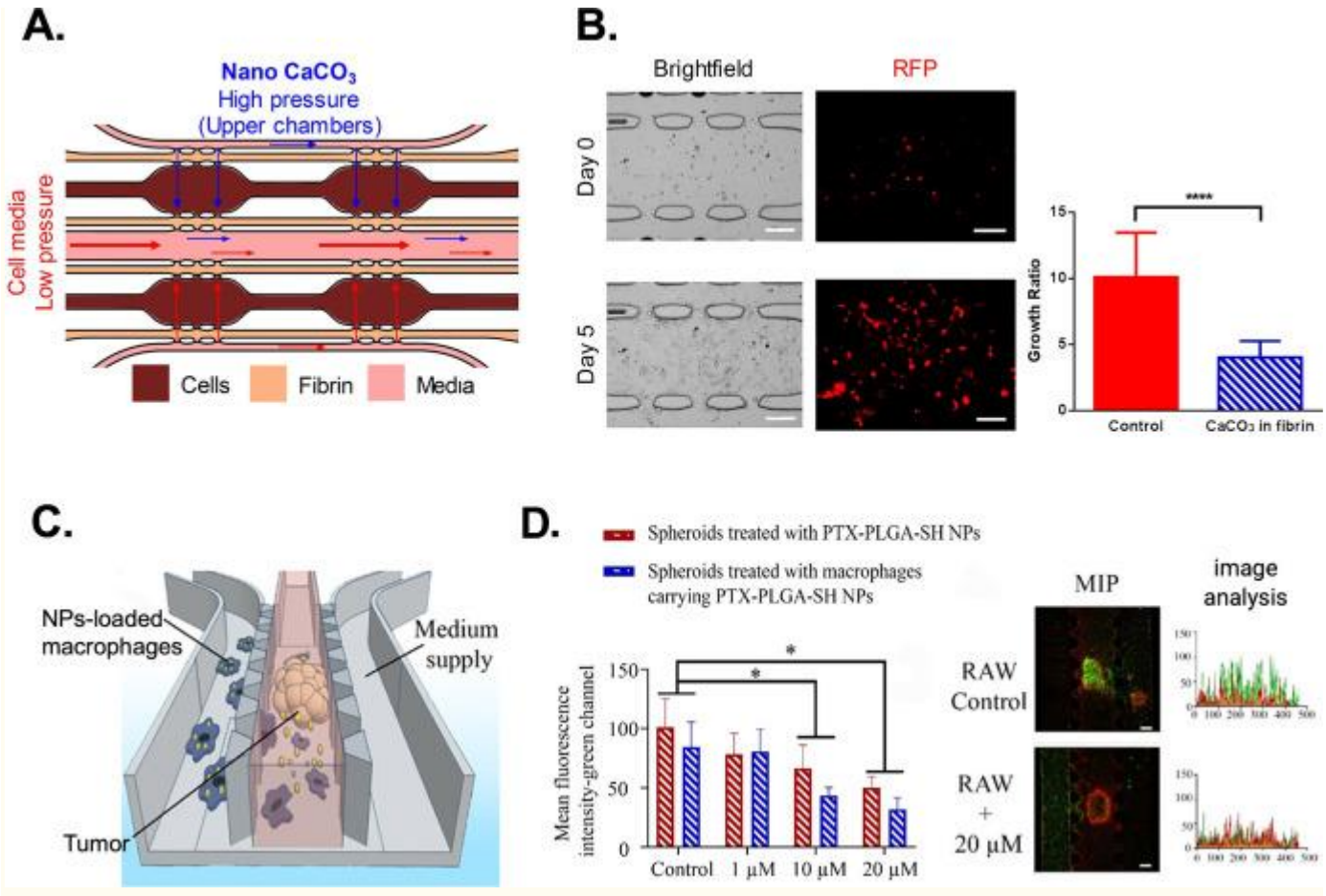
Legend for Figure 6:

courtesy ref no-219 Schematic analysis of the advantages and challenges of both static and dynamic cell cultures.



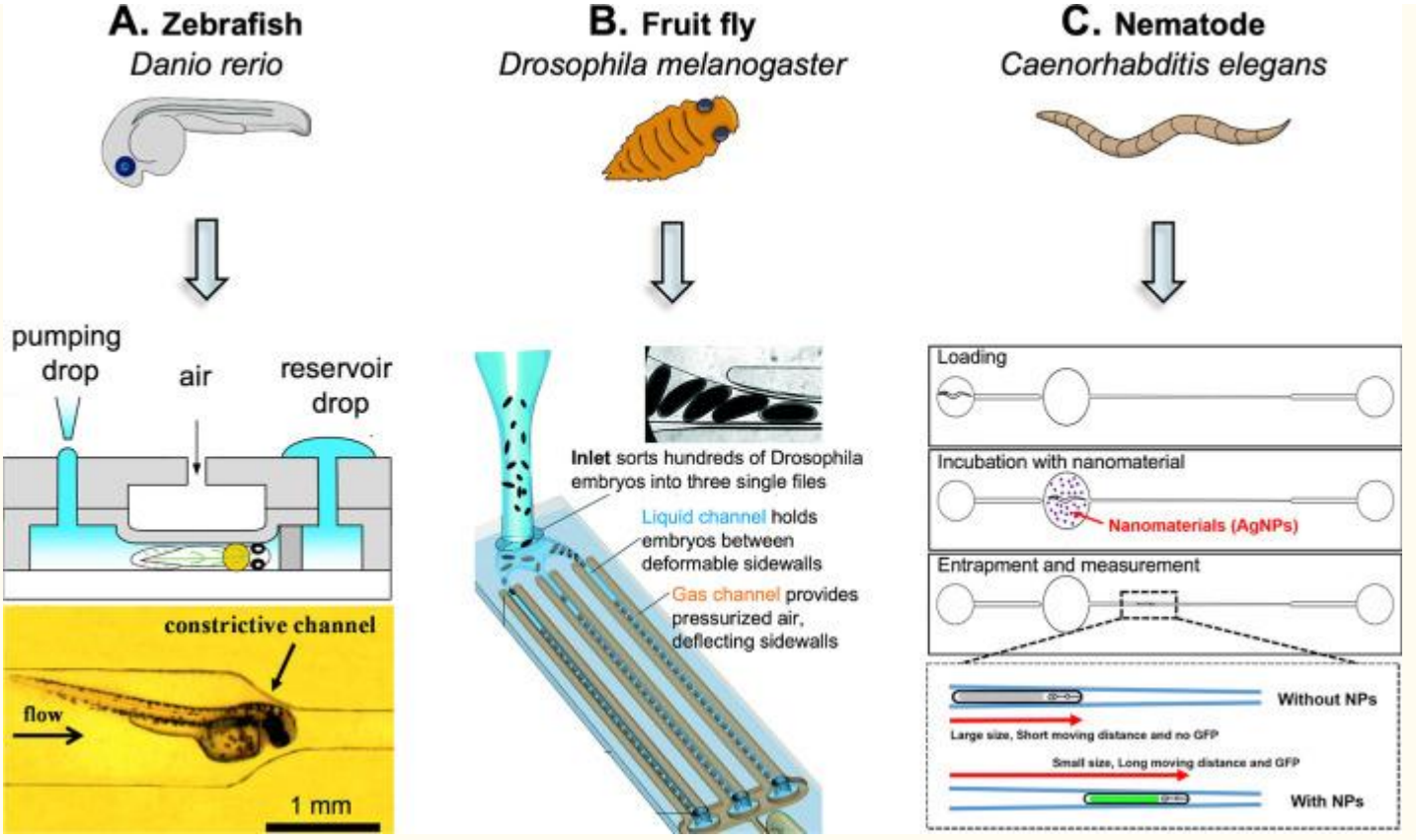
Legend for Figure 7:

Double-channel microfluidic device showing the vascular channel, seeded with HUVEC, and the extravascular chamber filled with Matrigel and collagen type I to represent the extracellular matrix (A - Adapted with permission from ref (rev in ref 219). Copyright 2021 Elsevier). Vascular permeability of polymeric nanoconstructs namely 200 nm polystyrene NPs (PB), soft discoidal polymeric NPs (sDPN), and rigid discoidal polymeric NPs (rDPN) in the absence of HUVEC (−HUVEC), with HUVEC (+HUVEC), with HUVEC treated with 1 M mannitol for 30 min and with HUVEC treated with 1 µM Lexiscan for 15 min (B - Reprinted with permission from ref (rev in ref 219). Copyright 2021 Elsevier). Microfluidic chip incorporating a series of six interconnected channels, which are linked to a peristaltic pump and a media reservoir (C - Adapted with permission from ref (rev in ref 219). Copyright 2020 Wiley). The uptake of NPs by HUVECs presents changes upon shear adaptation. HUVECs exposed to high shear rates have decreased capacity to uptake untargeted NPs (D - Reprinted with permission from ref (rev in ref 219). Copyright 2020 Wiley).



Legend for Figure 8:

A microfluidic device consisting of three sections was used to investigate tumor migration. The brown present MDA-MB-231 cells loaded in fibrin gels, while the adjacent chambers contain plain fibrin for measuring cellular migration. Inside the pink channel, culture media was flowing to nourish the tissue. The upper chambers will receive media containing CaCO3 nanoparticles, whereas the lower chambers will receive plain media (A - Reprinted with permission under a Creative Commons CC BY License from ref (rev in ref 219). Copyright 2021 Springer Nature). The treatment with nanoCaCO3 caused inhibition of breast cancer MDA-MB-231 cell line growth and migration (B - Reprinted with permission under a Creative Commons CC BY License from ref (rev in ref 219). Copyright 2021 Springer Nature). The microfluidic device integrates three microchannels separated by two lines of trapezoidal PDMS pillars. This setting enables the independent loading of hydrogel into each channel, facilitating the cultivation of tumor spheroids and macrophages in separate compartments while allowing substance exchange and intercellular crosstalk (C - Reprinted with permission from ref (rev in ref 219). Copyright 2020 American Chemical Society). Confocal images showing the cell viability of tumor spheroids and corresponding image analysis. The spheroids treated with PTX-NPs-macrophages exhibited higher mortality rates compared to the treatment with PTX-NPs alone (D - Reprinted with permission from ref (rev in ref 219Copyright 2020 American Chemical Society).



Legend for Figure 9:

Illustration of microfluidic technology application for small animal testing. Microfluidic devices have been developed for the accurate handling of zebrafish (A - Reprinted with permission under a Creative Commons CC BY 4.0 License from ref (rev in ref 219). Copyright 2015 MPDI), fruit fly (B - Reprinted with permission from ref (rev in ref 219). Copyright 2019 Royal Society of Chemistry), and nematode (C - Reprinted with permission under a Creative Commons CC BY License from ref 219 Copyright 2017 Springer Nature).

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