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Engineering precision biomaterials for personalized medicine

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Abstract

As the demand for precision medicine continues to rise, the “one-size-fits-all” approach to designing medical devices and therapies is becoming increasingly outdated. Biomaterials have considerable potential for transforming precision medicine, but individual patient complexity often necessitates integrating multiple functions into a single device to successfully tailor personalized therapies. Here, we introduce an engineering strategy based on unit operations to provide a unified vocabulary and contextual framework to aid the design of biomaterial-based devices and accelerate their translation.

DEFINING A PRECISION BIOMATERIAL

Precision medicine is a movement in clinical practice to develop treatments that are specific to an individual or subsets of patients (1). Former U.S. President Barack Obama launched the Precision Medicine Initiative in 2015, highlighting the limitations of a “one-size-fits-all” approach to medicine (2). Personal characteristics such as gender, age, and ancestry are often considered by clinicians when treating patients; however, disease progression is further affected by an individual patient’s biology, which may be difficult to incorporate into a patient-specific treatment plan using existing therapies. Because of challenges in accounting for individual complexities, patients often receive treatments that alleviate symptoms but do not address underlying disease etiology. A recent report estimates that the precision medicine market size in the United States will rise from \$39 billion in 2015 to more than \$87 billion by the year 2023 (3), indicating a sharp increase in demand for precision medicine technologies.

Addressing the increasing demand for precision medicine may require advances in biomaterials research that enable innovative product designs to target and treat various diseases. Current precision medicine strategies include collecting biopsies from cancer patients to analyze the genetic framework of the disease or transplanting patient-specific chondrocytes to repair cartilage defects. Despite growth in these personalized treatments,

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limitations remain, which hinder broader translation and impact, such as extensive sample processing, high cost, and inefficient delivery systems. Biomaterials underpin numerous precision medical devices such as sustained drug delivery systems (DDS), in situ bioanalytical tests, and implants that boost endogenous tissue repair. As precision medicine moves forward, new biological and drug products will necessitate new material-based devices to deliver them, and these devices will require precision biomaterials capable of interacting with the biology of the patient to elicit desired and predictable outcomes.

A precision biomaterial device uses customized material chemistry, device fabrication, bioactive components, and/or patient data analysis to detect or treat disease or injury in a specific patient or subsets of patients (Fig. 1). Precision biomaterials adapt to the patient with precise and specific functions. To date, the adaptive properties of most drug delivery, regenerative medicine, and diagnostic technologies that enable precision medicine rely on single or very simple building blocks. Future personalized treatments may require the combination of multiple building blocks that function in a precise manner—for example, recognizing a receptor, responding to the environment, releasing one or more payloads, and degrading at a desired rate. There is a growing appreciation that the biology of the host and implanted device directly affect each other; the challenge is to understand these interactions in sufficient quantitative detail to select design variables that allow coordination of a complex series of events based on the biology of the individual patient.

UNIT OPERATIONS APPROACH TO PRECISION BIOMATERIAL DESIGN

Here, a strategy is presented to codify the development of precision biomaterials and categorize their representative building blocks as unit operations. In engineering fields, a unit operation is a basic step or single function performed in a complex process. Engineers integrate multiple unit operations in the design of processes to manufacture products. We envision an analogous approach to the design and function of basic units that could then be combined to develop precision biomaterial devices. For example, toward patient-specific therapies, the unit operations approach could apply engineering principles for fabricating biomaterial devices to detect complex biological, chemical, and mechanical profiles specific to an individual, and then respond by orchestrating personalized treatments in real time. A rationalized strategy toward design should accelerate the development of unique devices, meet the demand for treating individual patients more effectively, and provide a unified vocabulary for researchers and clinicians in designing biomaterial-based devices for precision medicine.

Toward this concept, we provide five examples of biomaterial unit operations (Fig. 2). First, a biomaterial separator unit allows selection of a signal (small molecule, protein, exosome, or cell known to be involved in disease progression) from a complex milieu for detection purposes. Second, a sensor unit operation can detect a unique signal and/or quantify variations in that signal, for example, detection of specific analytes or enzymes in a local tissue or monitoring of changes in local concentration over time. Third, responder units deliver a biochemical payload and/or change a physical property in response to a signal in the local environment. The responder unit operation has a feedback mechanism where the biomaterial degrades or swells in response to local changes in enzyme concentration or pH,

subsequently releasing a therapeutic payload to the local environment. Fourth, controllers deliver a signal (drugs or cells) to induce a change in the local microenvironment—often with the goal of intervening in a tissue process that has gone awry, such as tumor growth or non-healing fracture. Controllers operate through a feed-forward design and allow for the dynamic exchange of information between the biomaterial and the implant microenvironment, which can amplify or attenuate the biological response. Fifth, a downstream unit processor enables the high-throughput in situ analysis of multiple variables to provide an overview of a patient's condition. Large data sets detailing patient information could be collected and organized using ontological analysis tools, pathological scoring, or other computational methods and reported directly to the clinician to provide an optimal path to therapy for a patient. Multiple unit operators may be combined within a single device to elicit complex, personalized functions and could provide a logical path toward development of biomedical devices for treating patient-specific disease or more fully characterizing the health status of a patient.

Several fundamental technologies currently available for designing precision biomaterials are equally important for developing precision unit operations. Advances in high-throughput omics and microbiome research have enabled new insights into the heterogeneity of disease and response to treatments (4), indicating an opportunity for using metadata to enable patient-specific treatments to be administered and processed on an implanted device. Gene editing and cellular reprogramming may enable new patient-specific cellular therapies (5), and precision biomaterials can play an important role as cell delivery vehicles to control cellular viability and engraftment after transplant. Additionally, three-dimensional (3D)/4D additive manufacturing (6), microfabrication (7), and nanoscale lithography (8) have begun to address the complexities required for manufacturing precision biomaterial-based devices across many length scales. Advances in material chemistry allow for bio-orthogonal reactions for a diverse array of biomaterial properties, including modulation of mechanical properties, incorporation of biological functionality, temporal control of properties such as degradation, and responses to local analytes or environmental conditions (9). New approaches for in situ monitoring of organ-on-chip systems may provide real-time evaluation of patient-specific organoid response to drug compounds (10). Novel computational approaches may determine dosing frequencies for immunosuppression treatments after liver transplants, indicating an opportunity to use sophisticated artificial intelligence methods to optimize treatment options for individual patients (11). Integrating these seemingly disparate technologies to design precision biomaterials remains a considerable challenge, as does the selection of the most important design criteria for specific applications.

Placing the unit operations concept in the context of examples of advanced biomaterial technologies that have the potential to serve as future precision biomaterials platforms can help outline strategies and design principles that will guide the development of precision biomaterials. Here, we highlight the modular, unit operations approach to biomaterial design for both existing U.S. Food and Drug Administration (FDA)–approved chemistries and newer customizable platforms. We include examples of precision biomaterials capable of sensing, responding to, and controlling the local environment. Establishing standardized design terminology and principles while precision biomaterials are in their infancy will

simplify the design process for future research. Our vision is that the unit operations approach will accelerate advancements in precision medicine and that devices based on precision biomaterials will have the potential to make disease or the risk of disease evident sooner, make treatments more successful, and prevent some diseases altogether.

CUSTOMIZING BIOLOGICAL INTERACTION AND CLINICAL DATA MONITORING WITH UNIT OPERATIONS

Precision medicine requires accurate assessment of a patient's condition to determine the most optimal therapy. Patients classified with equivalent stages of disease progression may exhibit remarkably different outcomes after treatment due to disease heterogeneity. Clinicians therefore require real-time patient evaluation and in situ monitoring of disease evolution, detection, and treatment. Recent examples of scaffolds, hydrogels, and particles fabricated from FDA-approved materials show that biomaterials separate, sense, or control resident cells or biologics and process relevant markers in situ. Using a bottom-up approach, patient-specific information obtained from noncustomized, off-the-shelf devices may be used to treat a patient more effectively or be used as a vehicle to deliver personalized therapeutics.

Cancer cell separation units

An off-the-shelf biomaterial can be used as a precision device for diagnosing and treating metastatic cancer. Metastasis progression varies between patients, and it can be challenging to detect the disease at early stages and administer customized treatment plans. Implantable poly(lactide-co-glycolide) (PLG) scaffolds captured metastatic cells in vivo in a mouse model of triple-negative breast cancer (12). The porous PLG scaffolds had inherent separator functions, capable of capturing metastatic cells before their arrival at target organs. Metastatic cell trafficking to the scaffold relies on previous recruitment of inflammatory immune cells known to participate in premetastatic niche formation, which enabled the diversion of metastatic cells toward an ectopic site away from traditional colonization sites at organs. In situ imaging of the implant using inverse spectroscopic optical coherence tomography enabled early detection of tumor cell recruitment to the scaffold, thus providing a path toward patient-specific determination of early metastatic events. In a future setting, porous scaffold separator units integrated with biomaterial sensor units could be implanted in breast cancer patients to capture disseminating tumor cells for downstream analysis of regulatory pathways governing patient-specific disease progression (13). This precision medicine-based approach may provide insights into differences in metastatic disease progression based on a patient's specific characteristics (age and ancestry) and could identify the most effective therapy for combating metastatic spreading within the patient.

Drug delivery responder units

DDS are analogous to many unit operations (sensors, responders, and controllers), and precision biomaterials could improve existing DDS. For example, patients often receive drug formulations that are not optimized for dose or frequency, requiring multiple visits with physicians to tune these variables over time. Drugs are metabolized differently by male and female patients, prompting investigations into sex as a biological variable in preclinical

trials. Recognizing these and other issues, DDS are being revamped to more precisely tune delivery kinetics for individual patients (14). For example, drug-loaded poly(ϵ -caprolactone) (PCL) oral capsules, an off-the-shelf material, were processed to respond to the acidic conditions in the stomach and self-expand into star-shaped drug delivery depots (15). The depots are too large to pass from the stomach to the intestine, which slows the release of the drug, potentially reducing patient burden of taking multiple drug doses during treatment. In future iterations of precision DDS, a unit operations approach could design controller functions that tightly regulate drug release over time according to patient sex, age, enzyme concentrations, or environmental factors. Precision biomaterials that sense very small changes in a patient's conditions (temperature, pH, and protein concentration) and respond by amplifying a change in a material property (dimensional change) could be used as an integrated sensor-responder to monitor a patient's condition during drug treatment.

Immune cell controllers

In addition to drug-based therapies, advances in precision biomaterial design enable the manipulation of transplanted or endogenous cells. Clinically used poly(ethylene glycol), collagen, and hyaluronic acid-based hydrogels are being explored as platforms to deliver patient-derived cells and/or provide signals to endogenous cells for promoting patient-specific healing. In one example, macroporous alginate scaffolds functionalized with collagen mimetic peptides served as a T cell-producing controller “factory,” providing mechanical and biochemical cues to support transplanted T cell survival, proliferation, and function to eradicate metastases and inoperable tumors (16). In a tissue regeneration approach, implanted cardiac muscle-derived extracellular matrix scaffolds stimulated a T helper 2 cell response in volumetric muscle defects (17). In more advanced precision devices, one might imagine the ability to sense disease or injury stage in a patient and then engineer the implant to more precisely control the required stimulation and release of patient-specific cells for therapy or regeneration of an injury site.

In situ processors to optimize drug combination therapy

Precision-based strategies to identify optimally effective drug formulations are in high demand. Innovative biomaterial technologies are emerging to select chemotherapeutics at desired concentrations and in appropriate combinations to combat tumors. A resin-based precision microdevice was designed as an implantable, retrievable DDS that responds to the tumor microenvironment by releasing microdoses of multiple chemotherapeutics such that efficacy can be assessed upon retrieval (18). In another approach, liposomes containing individual microdoses of different chemotherapeutics were tagged with a DNA “barcode” and delivered *in vivo* to target tumors (19). Upon assessing the tumor, the DNA barcode within dead cells corresponded to the most effective drug for treating the specific tumor. Quantitative analysis of tumor cell death *in situ* in response to multiple drugs administered simultaneously may help identify drugs most efficacious at inducing tumor cell death in the context of the patient’s tumor microenvironment. Another notable processor example is implantable silicon devices (20) that may advance the development of sensors for real-time monitoring of a patient’s vitals and how they may react to certain drugs.

CUSTOMIZING MATERIAL CHEMISTRY AND DEVICE FABRICATION BASED ON PATIENT-SPECIFIC INFORMATION

Off-the-shelf materials provide solutions for precision medicine that are closer to clinical translation, but some medical problems are better addressed by customization of the material itself. Designing customized devices for an individual patient follows a top-down approach, where patient-specific information informs the biomaterial design. The biomaterials community has pursued long-term, complementary approaches to design new biomaterial chemistries and reactions that integrate biological functionality, can respond to multiple stimuli, carry multiple drug payloads, sense and adapt to the microenvironment in vivo, protect hard-to-deliver cargos, and even have hierarchical “living” tissue-like functions such as self-healing. When combined with clinical or metadata from a patient or subsets of patients, these materials can be precisely designed for customized applications (21). Patient-specific characteristics such as age (22) and the diseased tissue microenvironment (23) may also affect the inflammation response and functionality of an implanted material. Consideration of patient-specific factors for biomaterial design may provide a critical bridge toward customized devices.

Tissue health assessing sensor units

Beyond macroscopic dimensions and fit, precision biomaterials must also adjust the molecular design of material formulations depending on patient characteristics. Tissue microenvironments are dynamic, and conditions such as disease or elevated inflammation can alter surface chemistry of an implanted device, affecting biomaterial adhesion and integration. One approach used fluorescent microspheres as sensors to evaluate amine density in healthy and diseased colorectal tissues and constructed a predictive processor strategy to determine the proper aldehyde content in dendrimer/dextran hydrogels for optimal adhesion strength (23). This biomaterial adhesive enhanced healing when combined with sutures in vivo in colon cancer and colitis models, and this approach could potentially be used in a clinical setting to rapidly analyze colorectal biopsies for amine density to select patient-specific material formulations. Developments in hydrogel sensor technologies could reduce the need for invasive diagnostic procedures (24). Future iterations could also integrate responders that release therapeutic small molecules upon contact with the diseased microenvironment.

Separator-processor units for assessing disease state

Individuals react differently to biomaterials after implantation, especially with respect to inflammation and protein deposition on the material. Macrophages from obese patients demonstrated a higher proinflammatory response to materials such as polypropylene and poly(lactic acid) in vitro (25). Other studies have focused on how a patient’s unique pathological condition affects the protein corona, defined as the composition of proteins associated with a nanoparticle, by examining a range of diseases (hemophilia and hypercholesterolemia) and conditions (smoking and pregnancy) using polystyrene and silica nanoparticle separators to collect serum proteins for downstream proteomic processing to determine potential disease markers (26). Such disease- and environmental-induced

differences may affect interactions of cells with nanoparticles and may inform selection of biomaterial chemistry for customized materials. In another study using porous collagen scaffold separators, markers in the protein corona were assessed by gel electrophoresis and mass spectrometry to correlate markers to a patient's secretome, indicating disease state or injury (27). To leverage the individual reactions, responders or controllers could be integrated into future biomaterial designs to ensure consistent performance despite patient-to-patient heterogeneity in the protein corona.

Adaptable biomaterial responder units

Customizing material designs for patients will also rely on advances in material chemistry, particularly the development of material systems to adapt to external and internal environmental changes. As an example of an external stimulus that can be controlled by a physician, a custom-designed hydrogel patch for local colorectal cancer treatment was designed with integrated sensor, responder, and controller functionalities (28). Gold nanorods loaded into the patch sensed tumor cells with targeting peptides for uptake and then responded to near-infrared (IR) irradiation to release antibodies to modulate the vascular endothelial growth factor pathway. Gold nanospheres with targeting peptides could then deliver small interfering RNA to control the oncogene driver Kras to treat and prevent cancer recurrence in a mouse model. This approach relied on a controlled external stimulus (near-IR light) to stimulate a biomaterial response, which may be a beneficial strategy for tunable, on-demand payload release.

Implanted precision biomaterials should also adapt to acute changes (tissue healing) and long-term changes (aging) within the internal microenvironment of a patient's tissue. Advances in hydrogel synthesis using reversible cross-linking chemistries can help develop responsive self-healing materials, where a hydrogel can be press-fit (29) or injected (30) into a defect to adapt as the injury heals, providing dynamic mechanical support of a tissue injury. Future advances in supramolecular and bio-orthogonal click chemistry could merge multiple unit operations, enabling both on-demand tuning of biochemical signals and mechanical properties based on patient needs, and materials that adapt, grow, and develop with the patient (31). As the toolbox of biomaterial chemistry expands, one can envision the development of a modular system in which specific unit operations can be selected and easily incorporated into a personalized material with desired functions.

CHALLENGES FOR PRECISION BIOMATERIALS

Degree of customization

One of the central challenges of developing a precision biomaterial device for clinical use is determining the degree of customization required. The decision to design simple off-the-shelf and complex customized biomaterials will lie at the intersection of multiple criteria, including (i) patient demographics, (ii) clinical need, (iii) disease and/or injury state, (iv) practicality, (v) ease of approval, and (vi) cost. Off-the-shelf materials can be mass-produced and cost-efficient, because they do not require patient-specific design. Custom-designed materials may provide the most precise treatment for a patient but may be expensive and difficult to obtain regulatory approval for use. Thus, precision biomaterial design will likely

lie on a spectrum—one where material, biological, device, and readout customization can be adjusted based on a patient's needs (Fig. 1). We anticipate that off-the-shelf materials will continue to be used in devices meant for rapid translation in the near term; however, material customization will play an important role in addressing complete and unmet patient needs in the long term.

Material interactions in patients over time

Precision biomaterial properties will likely be affected as a patient heals from injury or if a patient contracts or has an existing disease. Strategies to evaluate patient-material interactions will be paramount for the successful implementation of precision biomaterials. Clinicians will require improved materiomics techniques (21) to filter patient data to determine the most critical characteristics that inform and inspire precision material design using unit operators. Multiple variables (concentration, mechanics, and dosage) make it difficult to screen every possible combination for every patient. To address this issue, rapid and high-throughput techniques to screen how material properties may affect the biology of a patient are quickly emerging. For example, dip-pen lithography can be used to generate libraries of custom nanoparticles (8), and automated liquid handling can be used to build arrays of cell-laden hydrogels in a high-throughput fashion (32). These screening methods, especially when combined with rational design principles, should minimize barriers to the rapid assessment of patient-derived cellular response on many materials at once to help determine optimal material formulations for a patient.

Regulatory approval

Precision biomaterial devices with multiple unit operators may encounter challenges during regulatory approval. As multifunctional implantable devices move through preclinical animal models, the FDA must consider the risks of precision biomaterials against the protection of patient life. Simple devices using single unit operators and FDA-approved materials may achieve more rapid approval for clinical use and could improve current precision medicine strategies. For instance, clinical trials that rely on genomics to screen for an optimal drug therapy to treat cancer do not traditionally address problems associated with drug release kinetics or identifying the optimal drug combination for a specific patient. Simple drug responders could be designed and approved to address demands for patient-specific extended, sequential, or combinatorial drug release (14). In another vein, material microenvironments can be optimized for mesenchymal stem cell (MSC) expansion for regenerative medicine clinical trials. MSCs become more osteogenic when cultured on tissue culture polystyrene (33), indicating an opportunity for using tunable precision materials to control MSC proliferation, multipotency, and secretory properties while retaining the regenerative capacity of a patient's MSCs in vitro. Addressing immediate limitations in current clinical trials using individual unit operations may accelerate the approval of precision biomaterial systems that use multiple unit operators simultaneously.

Data management and interpretation

The implementation of precision biomaterials in the clinic will also face challenges with interpreting, organizing, and managing large data sets. Accurate and safe data sharing between clinicians and manufacturers will be critical for generating optimal devices for

patients. Patient-specific data sets come in many forms, from real-time monitoring of a single bioanalyte to comprehensive characterizations of a patient's biological composition. Data sets from large populations of patients such as the National Institutes of Health (NIH)–funded “All of Us” Research Program could be used to determine the specific therapeutic needs of subsets of patients with certain demographics and disease states. Although analyzing data sets from individual patients may generate optimally customized devices, a higher-throughput approach analyzing data sets from millions of patients may also provide sufficient insight to inform material design for an individual patient's device.

As such, the precision biomaterials community must also acknowledge limitations in interpreting high-throughput data sets for the design of complex materials using unit operations. Previous work has shown that genomewide screens may not always correlate to a patient's phenotype, as numerous variables such as the transcriptome, proteome, and metabolome may influence phenotype as well. Novel approaches in “systems medicine” seek to understand the regulatory networks of disease state for individual patients (34), which may provide additional insight toward developing more effective biomaterials to manipulate these pathways. Translation of future devices for a specific patient or subsets of patients will depend on achieving a global view of a patient's condition using facile regulatory network analysis and artificial intelligence approaches, and learning how implanted devices may affect the regulatory network of disease within a patient.

CONCLUDING REMARKS

Our unit operations approach is a call to action for researchers and clinicians in the precision medicine space to develop rationalized strategies for addressing patient-specific variables using advanced biomaterial devices. With a unified vocabulary for precision biomaterial design, researchers and clinicians can begin to identify the device-specific unit operators, with the goal of accelerating device innovation at all stages—from concept to mass production. As the precision biomaterial field continues to evolve, additional unit operators—for example, reactors to break down cholesterol in situ—may be added to the design toolbox. Permutations of devices designed with numerous unit operators can provide ultimate customization, whether using existing FDA-approved off-the-shelf materials or newer customized materials. Although several regulatory hurdles limit widespread translation of customized devices for individual patients, precision biomaterials have the potential to address the most pressing limitations of using personalized medicine strategies in the clinic. Investing resources in the development of precision biomaterials may also usher in an era of living materials that integrate with a patient's body and alter their properties at multiple length and time scales to meet the demands of maintaining health as the patient ages (35). Together, the implementation of unit operations to design precision biomaterials will continue to inspire new applications, address translational barriers, and provide innovative solutions in precision medicine.

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Criteria for precision biomaterial design

Fig. 1. Criteria for precision biomaterial design.

Design parameters lie on a spectrum, where the desired amount of customization (triangle with red gradient) can be tuned from little/none (multiple people) to complete personalization (single person) to yield a precision biomaterial device. (A) Material chemistries may be customized for devices, including DDS. Small molecules may passively release from a basic polymer network, whereas enhanced customization may produce a polymer network that releases drugs in response to a stimulus (low pH). Patient-specific drug therapies may use materials that release drug combinations in response to patient-

specific enzymes. **(B)** Precision biomaterials may be fabricated using basic porous scaffolds or may be 3D-printed to fit the defect of a specific patient. Adaptable materials that grow with a patient over time may be fabricated for further patient customization. **(C)** Bioactive components (such as cells) may be introduced to a patient using precision biomaterials, such as delivering noncustomized allogeneic transplants or personalized autologous transplants. For further customization, engineering patient cells may lead to more effective treatments for patient-specific diseases or injuries. **(D)** Patient data analysis may be facilitated using precision biomaterial devices, including devices that enable the ex vivo evaluation of a patient's biopsy. Biomaterial implants may also enable the in situ evaluation of a patient's condition over time or real-time tracking of response to therapy.

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Unit operations for precision biomaterial design

Fig. 2. Unit operations for precision biomaterial design.

Multifunctional unit operators can be combined in parallel or in series to design devices to control processes at the molecular, cellular, or tissue scale for an individual patient. (A) Separators can distinguish rare populations of bioanalytes, cells, etc. (for example, separating immune and metastatic cells using a poly(lactide-co-glycolide) scaffold in vivo). Figure adapted from (12). (B) Sensors can detect specific electrical, mechanical, or temperature signals, bioanalytes, or cells in a local tissue microenvironment (for example, fluorescent microspheres sense amine density in tissues from severe inflammatory colitis

and colon cancer models). Figure adapted from (23). **(C)** Responders release a therapeutic payload upon contact with a signal, which may serve as a positive feedback mechanism (for example, self-expanding poly(ϵ -caprolactone) capsules used for extended drug release). Figure adapted from (15). **(D)** Controllers induce changes in the local environment and reduce or stimulate the effect in a feed-forward fashion (for example, adoptive T cell therapy enhanced with alginate scaffolds that boost T cell proliferation and eradicate tumor cells in vivo). Figure adapted from (16). **(E)** Processors allow downstream analysis and organization of high-throughput results [for example, polymerase chain reaction (PCR) identifies gemcitabine as the drug that led to most cell death within breast tumors using DNA-barcoded chemotherapy-loaded nanoparticles]. Figure adapted from (19).