HHS Public Access

Author manuscript

Adv Drug Deliv Rev. Author manuscript; available in PMC 2022 April 01.

Published in final edited form as:

Adv Drug Deliv Rev. 2021 April ; 171: 1–28. doi:10.1016/j.addr.2020.11.009.

Automation and Data-Driven Design of Polymer Therapeutics

Rahul Upadhya[a], **Shashank Kosuri**[a], **Matthew Tamasi**[a], **Travis A. Meyer**[a], **Supriya Atta**[a], **Michael A. Webb**[b], **Adam J. Gormley**[a,*]

[a]Department of Biomedical Engineering, Rutgers, the State University of New Jersey, Piscataway, NJ 08854, USA

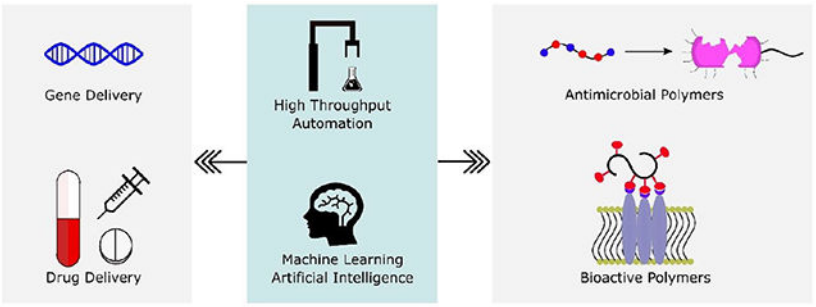
[b]Department of Chemical and Biological Engineering, Princeton University, Princeton, NJ 08540, USA

Abstract

Polymers are uniquely suited for drug delivery and biomaterials applications due to tunable structural parameters such as length, composition, architecture, and valency. To facilitate designs, researchers may explore combinatorial libraries in a high throughput fashion to correlate structure to function. However, traditional polymerization reactions including controlled living radical polymerization (CLRP) and ring-opening polymerization (ROP) require inert reaction conditions and extensive expertise to implement. With the advent of air-tolerance and automation, several polymerization techniques are now compatible with well plates and can be carried out at the benchtop, making high throughput synthesis and high throughput screening (HTS) possible. To avoid HTS pitfalls often described as “fishing expeditions,” it is crucial to employ intelligent and big data approaches to maximize experimental efficiency. This is where the disruptive technologies of machine learning (ML) and artificial intelligence (AI) will likely play a role. In fact, ML and AI are already impacting small molecule drug discovery and showing signs of emerging in drug delivery. In this review, we present state-of-the-art research in drug delivery, gene delivery, antimicrobial polymers, and bioactive polymers alongside data-driven developments in drug design and organic synthesis. From this insight, important lessons are revealed for the polymer therapeutics community including the value of a closed loop design-build-test-learn workflow. This is an exciting time as researchers will gain the ability to fully explore the polymer structural landscape and establish quantitative structure-property relationships (QSPRs) with biological significance.

Graphical Abstract

*Corresponding Author Adam.Gormley@rutgers.edu.



Keywords

Polymer chemistry; high throughput screening; automation; machine learning; artificial intelligence; drug delivery; gene delivery

1. Introduction

Polymers are central to a wide range of applications including drug delivery, gene therapy, antimicrobial therapeutics, and drug formulation. For instance, polymers can deliver bioactive molecules by improving circulation time and bioavailability, boost the solubility of hydrophobic drugs, and disrupt bacterial cell membranes [1–8]. They can also be utilized as scaffolds to present biomolecules or therapeutics such as proteins, peptides, nucleic acids, and small molecule drugs at a site of interest. With modern controlled living radical polymerization (CLRP) techniques, polymers have several tunable parameters – such as degree of polymerization (DP) or chain length [9–14], composition [10, 15, 16], architecture [9], stereochemistry [17, 18], compactness [19], and valency [9, 20] – that potentially enable polymer design for specific applications based on desired characteristics. Specific areas that can benefit from precision polymer design include gene delivery, drug delivery, antimicrobial polymer therapeutics, and bioactive polymers including polymer-peptide, polymer-nucleic acid, polymer-drug, and protein-polymer conjugates [8, 21–25]. As polymer design is often an unintuitive process, future developments in these areas would be facilitated by sophisticated approaches to high throughput study and data-driven design.

The domain of high throughput study can be separated into combinatorial chemistry, high throughput experimentation (HTE), and high throughput screening (HTS). In combinatorial chemistry, relevant parameters (e.g. solvent, material composition, and additives) are tested in a parallel manner. HTE involves testing of numerical variables such as temperature, pressure, time, and volume while HTS is parallel, rapid testing [26]. HTS initially expanded in the life sciences and pharmaceutical industries in the 1950s with widescale screening of small-molecule compound libraries [27–29]. More recently in the 21st century, there have been advancements of HTS techniques in biomaterials and drug delivery with an increased use of automation to conduct experiments [10, 15, 24, 30]. Historically, polymer chemistry has not progressed towards automation because of a need for reaction optimization and lack of polymer compositional flexibility, but this has changed dramatically over the past 5-10 years [9–14, 31–33].

Nonetheless, some have described these approaches as “fishing expeditions,” which can be fair criticism because HTS lacks experimental feedback, has a tendency to be influenced by personal biases, contains high risk for false positives and false negatives, and presents difficulties for intuitive data analysis or justification. There is a need for a feedback mechanism to pinpoint which study elements should be incrementally modified [34–37]. A reasonable selection process is also sought-after so a diverse combinatorial library can be prepared and efficiently sampled for hits [38, 39]. Illustrating this need for experimental feedback, over the time period when HTS became widely utilized in pharmaceutical drug discovery (1990-2013), the number of new chemical entities (NCEs) did not increase [40]. Limitations to HTE and HTS for polymers may be addressed through applications of artificial intelligence (AI) and machine learning (ML).

Traditionally, AI approaches to polymer design have been rarely considered. However, the present day is an exciting time for automation, AI, and ML, with applications emerging across sectors such as transportation, manufacturing, and healthcare. This has been aided by a greater emphasis on handling “big data” and an increase in academic interest (Fig. 1). In pharmaceuticals, interest in AI and ML has grown exponentially over the past decade, whereas the field of drug delivery seems to be approaching an inflection point. More specifically, collaborations between pharmaceutical and technology companies have led to the development of AI solutions to tackle healthcare challenges. Some examples include partnerships between Novartis/Pfizer and IBM Watson, AbbVie/Merck and Atomwise, Amgen and GNS Healthcare, GlaxoSmithKline/Sanofi and Exscientia [41]. Partnerships between academia and industry have also formed for the same purpose such as the Machine Learning for Pharmaceutical Discovery and Synthesis Consortium (MLPDS) between MIT, Merck, Bayer, AstraZeneca, Novartis, Pfizer, and others [42]. Further, AI strategies exist in about 16% of healthcare companies but in over 30% of technology companies [41]. This disparity represents an exciting growth potential for AI in the pharmaceutical industry.

Despite this potential, automation, AI, and ML are largely unexplored and unknown in the polymer therapeutics and biomaterials communities. This review aims to present current research on this topic related to polymer drug delivery. We will then highlight potential avenues by which HTS, automation, and data-driven design can be employed by studying its usage in organic synthesis of small-molecule pharmaceuticals. To conclude, we will offer a perspective on potential drawbacks and future trends.

2. Recent Advancements in High Throughput Technologies for Polymers

2.1. Early Efforts in High Throughput Polymer Chemistry

High throughput experiments are useful in the realm of polymer chemistry because important structure-property relationships can be identified by exploring a large chemical space. Initial work in this space in the 1990’s involved the usage of parallel synthesizer vessels with the capability to automatically prepare reaction mixtures in sealed vessels. Here, we will describe some of this early work that lays the foundation for the rest of this review.

As early work in HTS and combinatorial chemistry was being completed in the drug discovery space, the area of polymer chemistry was exploring the utility of this approach. This includes groundbreaking work in the late 1990s from Joachim Kohn's group which synthesized a large library of 112 degradable polyarylate copolymers in parallel reaction vessels [43, 44]. After thorough characterization, a structure-activity relationship was developed between the copolymer composition and hydrophobicity, flexibility, glass transition temperature (T_g), air-water contact angle, and cell proliferation. While this initial approach was promising, improvements could be made in terms of throughput and reaction control [32].

Schultz and Zaffaroni had the goal of increasing throughput and established Symyx Technologies in 1995 to provide platform technologies for high throughput polymer synthesis [26]. For instance, Bosman et al. created a library of 384 star polymers for reaction optimization by nitroxide-mediated radical polymerization (NMP) [45]. While the instrument automated preparation of reaction mixtures, it required a sealed reaction vessel, multiple freeze/thaw cycles, and precipitation purification which limited throughput. Chemspeed is another company that has developed tools for laboratory automation and HTE. The Chemspeed Accelerator SLT106 synthesizer can conduct 16 parallel reactions in glass vials using four pipette heads. However, the instrument has similar limitations as products from Symyx Technologies [46].

The progress made by Kohn, Schultz, Zaffaroni, and others introduced combinatorial polymer chemistry to a wider audience and made it possible for polymer science to branch out into various applications. For example, this was done in the field of drug and gene delivery through the works of Anderson, Langer, and others. Combinatorial and high throughput approaches allowed for the modulation of stem cell attachment, growth, and differentiation to polymers [47–52] and an improved understanding of material design parameters for degradability, mechanics, and surface characterization [53–55]. Early reviews on combinatorial chemistry and high throughput approaches in polymer chemistry related to biomaterials and materials science can be found separately [39, 56, 57].

2.2. Air-Tolerant Polymer Chemistry

To achieve the ambitious goal of building quantitative structure-property relationship (QSPR) models for polymer-based therapeutics, it is crucial to synthesize large polymer libraries to define the role and importance of various design parameters [32]. However, many of the early advancements described in Section 2.1 are not amenable to synthesizing and purifying large polymer libraries with fully automated workflows. The major obstacle to establishing more user-friendly polymerization techniques is air intolerance due to oxygen or humidity. In the past decade, progress has been made by multiple groups who have demonstrated open-air techniques for ring opening polymerization (ROP), RAFT polymerization, and atom transfer radical polymerization (ATRP) [31]. For more comprehensive information about this emerging field, see review [31].

ROP is a widely used technique for synthesizing biodegradable polymers such as polycaprolactone (PCL), poly(lactic acid) (PLA), and poly(lactic-*co*-glycolic acid) (PLGA) [58]. However, ROP suffers a severe limitation where polymerization must be conducted in

inert atmosphere as water impurities can cause lower molecular weight polymers [59]. To simplify the ROP method, scientists have investigated strategies by which ROP can occur in aqueous conditions. For example, Gleede et al. have reported ROP of *N*-sulfonylaziridines where the moisture tolerance arises from the generation of a propagated active chain that is stable in the presence of water and alcohol impurities [60]. Furthermore, Nagai et al. have developed a cationic ROP of 1,3-oxazolidine-2-thione using a water stable initiator methyl-trifluoromethanesulfonate [61]. Interestingly, Wu et al. have reported ROP of α-amino acid *N*-carboxyanhydrides (NCAs) in an open vessel using lithium hexamethyldisilazide (LiHMDS) as an initiator [62]. Each method utilizes specific monomers and conditions to achieve moisture tolerance. Therefore, it is important to develop a method for commonly used monomers such as lactide or caprolactone.

Recently, an oxygen-tolerant technique was reported by Matyjaszewski and others in which polymers of oligo(ethylene oxide) methyl ether methacrylate (OEOMA) were synthesized via enzyme-assisted initiators for continuous activator regeneration (ICAR) ATRP [14]. Glucose oxidase served as the enzyme that scrubs oxygen in the presence of glucose and sodium pyruvate. Controlled polymerization was demonstrated, achieving a dispersity ($Đ$) < 1.3. This technique was validated in open vials with as much as 25 mL in reaction volume. In addition, Truong, Anastasaki, and co-workers found that the selection of photoinitiated ATRP ligand, initiator, and solvent conditions affect oxygen consumption and thus reaction control [63].

Similarly, Stevens, Chapman, and Gormley introduced enzyme-assisted RAFT (Enz-RAFT) polymerization by which glucose oxidase was demonstrated to enable deoxygenation in open vessels [11]. Not only were they able to achieve controlled polymerization ($Đ$) < 1.15) but also synthesized polymers in aqueous and various aqueous/organic solvent conditions. They further demonstrated that this technique could be carried out in well plates, synthesizing various polymers composed of acrylate, methacrylate, acrylamide, and methacrylamide monomers in sealed 384-well plates with high control [12]. Another technique was developed by Boyer and others, termed photoinduced electron transfer-RAFT (PET-RAFT) [13]. Here, $Ir^{(III)}$ functioned as a photoredox catalyst alongside a thiocarbonylthio chain transfer agent (CTA). They synthesized several polymers consisting of acrylate, methacrylate, acrylamide, methacrylamide, vinyl ester, vinyl phosphonate, and *N*-vinyl pyrrolidinone monomers in ambient conditions without a deoxygenation step to initiate the reaction. Subsequent work was published on this subject [64–66] and on low-volume PET-RAFT in 96-well plates [9, 33].

Other polymerization techniques have also been recently adapted. In 2019, Gibson and others developed a tertiary amine deoxygenation photopolymerization technique that can be conducted in deep well 96-well plates in non-DMSO solvents (dioxane, methanol, and toluene) [67]; the proposed mechanism is that tertiary amines, such as triethanolamine and triethylamine, transfer electrons to the trithiocarbonate RAFT agent, which further reduces dissolved oxygen to superoxide. Although this technique cannot control molecular weight as well as PET-RAFT, it was used to synthesize about 400 polymers in less than 40 hours, demonstrating its potential utility as a rapid polymerization for screening (especially if organic solvent conditions are preferable). In addition, Gurnani et al. developed a PCR-

RAFT technique that is accessible for researchers in a biology laboratory, synthesizing water-soluble acrylamide polymers by heating in a 96-well thermocycler [68].

Despite the high throughput and air-tolerant polymerization techniques available, researchers in polymer science typically purify small-molecule impurities associated with polymerization or post-polymerization functionalization by labor-intensive precipitation and two-phase extraction [32, 69, 70] or overly complex high throughput preparative HPLC methods [71–74]. Scientists may even rule out purification because of these complexities [75]. Unfortunately, none of these purification strategies are amenable for preparing large polymer libraries. We recently published a gel filtration chromatography (GFC) technique with spin filtration columns that were pre-packed or manually packed with size-exclusion resin. Along with significant reduction of time and labor, we demonstrated a >95% removal of small-molecule impurities and >85% polymer retention for a library of 32 polymers [76]. An automated dialysis technique through the use of robotics to purify small-molecule impurities has also been recently reported by Schubert et al. [77].

In addition, by complementing high throughput PET-RAFT and gel filtration spin purification with high throughput polymer characterization by small-angle X-ray scattering (SAXS), we synthesized over 450 unique polymers (homopolymers, random heteropolymers, and block copolymers) and quantified features such as flexibility, compactness, and hydrophobicity [19, 76] to reveal a phase relationship between hydrophobicity of the polymer backbone and parameters related to compactness and flexibility.

In summary, various air-tolerant techniques have been established over the past decade including open vessel ROP, ICAR ATRP, Enz-RAFT, and PET-RAFT. More recently, progress has been made by our group and others to correlate structural attributes (DP, geometry, and polymer composition) to parameters of interest such as protein binding, flexibility, and compactness [9]. As synthesis, purification, and characterization tools such as the ones described in this section become more widely employed, we expect the progression of high throughput and combinatorial polymer chemistry approaches in the drug delivery and biomaterials community.

2.3. Conjugate Chemistry for High Throughput Testing

While development of small-molecule chemical scaffolds has been in practice for many years, only modest efforts have been made with macromolecules [78]. A major reason for this is the incompatibility of biologically relevant ligands with polymerization processes which necessitates steps for post-polymerization functionalization. This requires developing efficient conjugation strategies that are compatible with high throughput polymer synthesis, require non-toxic reagents, and can be performed under different reaction conditions. Current chemistries for efficient conjugation are Diels-Alder, thiolene, tetrazine-based cycloadditions and strain promoted azide-alkyne cycloaddition (SPAAC) using cyclooctyne derivatives such as dibenzocyclooctyne (DBCO) [79–81].

Tetrazene-norbornene conjugation reactions have been used to generate polymer-polymer conjugates and end-functionalized polymers in both aqueous and organic solvents. O'Reilly

and co-workers developed a one-pot “mix and click” reaction to synthesize double core-shell micelles combining RAFT with tetrazene-norbornene chemistry [83]. RAFT copolymerizations were completed to synthesize amphiphilic block copolymers with norbornene and alkyne functionalities which were subsequently dissolved in water to form micelles with a hydrophobic core and hydrophilic shell. Norbornene functional handles were conjugated to tetrazine compounds while alkyne handles were clicked to azide handles using copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) chemistry. This simple one-pot approach allows functionalization of water soluble azide-bearing handles to the micellar shell and hydrophobic-bearing tetrazine molecules to the core using two different orthogonal click reactions. CLRP can typically tolerate a low norbornene concentration because of its reactivity towards radicals, especially at high monomer conversion.

Another type of click reaction that has been widely used for polymer modification is the thiolene reaction. While the radical mechanism of thiol addition to alkenes has been known as early as the 1930’s, the utility of thiolene chemistry as a means for functionalization came to prominence much later. Initial applications were mainly focused on modification of natural rubbers and extensive research over the last few decades has resulted in a variety of post-polymerization substrate modifications [84]. However, thiolene chemistry has proven to be extremely challenging for CLRP approaches because of the reactivity of both thiols and alkenes under radical polymerization conditions. Hawker and co-workers demonstrated a way to work around this problem by copolymerizing monomers that have modifiable alkenes with vastly different reactivities [85]. Styrene and homoallyl functionalized styrene were copolymerized using ATRP and RAFT techniques resulting in polymers containing an allylic end which was used for subsequent thiolene conjugation.

SPAAC is often a preferable click reaction for bioconjugation because of cyclooctyne stability and high specificity towards azide-reactive groups. To synthesize functionalized polymers with SPAAC handles, NHS-activated esters are commonly used because of their ease of copolymerization as well as their ability to react with various chemical functional groups. Boyer and co-workers utilized this ability to synthesize different polymer architectures and study their effects on polymer binding, as described in Section 2.2 [9]. The post-polymerization functionalization began with incorporation of NHS-acrylate onto a polymer backbone using PET-RAFT. After polymerization, scaffolds were functionalized with a strained alkyne (DBCO-NH_2) which allows for further functionalization with any desired azide via SPAAC. For more information regarding post-polymerization functionalization using NHS-activated esters, see another review authored by Blasco and others [86].

Because click handles may be incompatible with CLRP, the majority of these click functionalities are either introduced post-polymerization or need to be chemically deprotected [87, 88]. Popik and co-workers developed a cyclopropenone masked dibenzocyclooctyne (cp-DIBAC) that is photoactivated with UV light resulting in deprotection and generation of strained cycloalkyne [89]. The masking of DIBAC with a cyclopropenone group renders it compatible with CLRP. Qu et al. then synthesized linear polymers incorporated with cp-DIBAC by RAFT and ATRP [90–92].

Expanding on these studies, our lab in collaboration with Robert Chapman's group, recently developed a single, one-pot, dual-wavelength procedure for synthesizing SPAAC-ready linear or star-shaped polymers [20]. We hypothesized that cp-DIBAC would be compatible with PET-RAFT to generate conjugated polymer libraries (Fig. 2). We synthesized cp-DIBAC either into the side chain of linear polymers or into the Z group of a CTA to produce end-functional polymers. Deprotection at an orthogonal wavelength (350 nm) followed by click addition to azido ligands resulted in generation of bioactive polymers in 96- and 384-well plates in DMSO. The cyclopropenone masking nature of cp-DIBAC allows an interesting dual-functionalization strategy that can be utilized for clicking multiple ligands onto polymers. To illustrate this, we generated polymers with two functional handles via DBCO and DIBAC chemistries. The resulting polymers and conjugates showed excellent control of molecular weight, $Đ$, conversion, and click efficiency. We also investigated the use of cp-DIBAC for making end-functionalized 2-, 3-, and 4-arm star polymers. Click-versatility was exhibited by preparing functional polymers containing bioactive peptides. In addition, we demonstrated the high throughput capability of the system by synthesizing a library of 80 linear polymers in 384-well plates with different chain lengths and valency. The resulting polymers and conjugates showed excellent control of molecular weights, $Đ$, conversion, and click.

3. Expansion into Automation and Data-Driven Design

3.1. Robotics and Automation

Combinatorial, HTE, and HTS approaches were adopted as early as the 1980s in the biological sciences. For instance, parallel synthesis and screening of peptides along with polysaccharides and nucleic acids were initially investigated [26]. High throughput techniques were also introduced to the pharmaceutical sciences through the screening of large drug compound libraries [26, 93, 94]. Major benefits of incorporating automated instruments into experimental workflows include accelerating repetitive tasks and limiting exposure to potentially harmful materials while improving reproducibility [95]. Automation technologies have also been integrated into several high throughput workflows, namely in the life sciences where liquid handling instruments simplify serial dilutions, endpoint and kinetics assays, and aliquot creation. In this section, we review more recent developments made in robotics and automation adapted for polymer chemistry.

A high throughput, automation-friendly approach is not often utilized in polymer chemistry and biomaterials. In numerous cases, automation and robotics have been used for optimizing reaction conditions rather than synthesizing and screening large libraries of bioactive materials [26, 93, 94, 96]. This is due to the low throughput nature of traditional polymer synthesis, which has left the chemical landscape largely unexplored. As a result, there is a need to conduct polymer synthesis, characterization, and screening experiments in a parallel fashion rather than in a one-factor-at-a-time (OFAT) manner [26, 96–99].

Some automation technologies exist to conduct ROP in a high throughput fashion. Hoogenboom et al. first developed an automated synthesizer in which the ROP of 2-ethyl-2-oxazoline was performed in inert atmosphere conditions [100]; they achieved polymer libraries of 40 parallel polymerizations at 8 different monomer:initiator ratios. Furthermore,

they have developed a microwave-assisted automated method for ROP of 2-oxazolines [101]. Waymouth and co-workers more recently have developed an automated high throughput continuous-flow reactor for ROP of polylactones [102]; they employed urea anion catalysts for the rapid generation of a library of 100 distinct homopolymers and block copolymers in less than 9 minutes.

There have also been numerous developments in the instrumentation and techniques related to combinatorial high throughput polymerization. For instance, Schubert and co-workers demonstrated the utility of a high throughput approach for synthesis of polymers by RAFT and anionic polymerization along with process development [103]. Specifically, they evaluated the Chemspeed ASW2000, Chemspeed Accelerator SLT100, and Chemspeed A100. Schubert and others further compared these synthesizers based on achievable molecular weight, dispersity ($Đ$), and reproducibility [104]. Overall, depending on the set of reaction conditions, the automated synthesizers either displayed similar or improved performance relative to a manually-performed reaction. In 2012, Guerrero-Sanchez et al. established a freeze-evacuate-thaw degassing method that could be used to prepare combinatorial polymer libraries in parallel reactor blocks [105]. Similar approaches are still taken in the present day, as illustrated by work from Saldivar-Guerra and co-workers from 2019 [106]. This group conducted a semiautomated polymerization of copolymers containing isoprene and glycidyl methacrylate via RAFT polymerization. As was the case with previous synthetic workflows, pressurized parallel reaction vessels were needed with constant flow of nitrogen. Unfortunately, many of the same issues exist such as workflow inefficiencies along with a difficulty to optimize reaction conditions and purify. Reviews that discuss traditional combinatorial and high throughput polymerization techniques [107, 108] and high throughput synthesis equipment [109] have also been published.

An early application of automation in gene delivery was revealed by Anderson et al in 2003 [110]. In this landmark work, a large library of 2350 poly(β-amino ester)s (PBAEs) were synthesized by Michael addition of amines to diacrylates. These cationic polymers were prepared in DMSO and diluted directly for *in vitro* experiments to assess transfection efficiency. An important experimental consideration raised was that it is preferable to synthesize the polymer library directly in 96-well plates because downstream cell culture experiments are also conducted in well plates. 486 polymers were further characterized to illustrate that three factors affect transfection efficacy: polymer-DNA complex size, polymer end group, and zeta potential [111]. This facilitates the usage of automation for plate-to-plate transfers and serial dilutions. In addition, for liquid handling robotics, a modular workflow is preferable because it can be versatile and accessible [97, 112, 113]. For structurally diverse libraries, a synthetic route with robust reaction conditions and a scaffold-based approach aids in maximizing efficiency [34].

With automation playing a crucial role in the development of combinatorial polymer libraries, our group recently investigated the potential of combining oxygen-tolerant Enz-RAFT and PET-RAFT chemistries with a Hamilton MLSTARlet liquid handling robot [10]. Leveraging the high level of customizability of the Hamilton MLSTARlet, Python scripts were generated to create automated chemistry routines based on the literature. These scripts took input polymer design parameters of material composition, DP, and chemistry (Enz-

RAFT or PET-RAFT) and transformed the information into reagent lists, volumes, and sequence instructions for the Hamilton MLSTARlet. Utilizing this system, we demonstrated the ability to synthesize both homopolymers and block co-polymers in 96 well-plates by robotic PET-RAFT and homopolymers by robotic Enz-RAFT (Fig. 3).

We also used this system to implement multi-step post-polymerization modification starting with NHS-acrylate in the copolymer backbone. NHS-acrylate containing copolymers were then automatically post-functionalized by addition of DBCO-amine, enabling PEG-azide to be attached to the polymers through SPAAC click-chemistry (Fig. 4). Furthermore, while the flexibility of highly versatile liquid handling robotics like the Hamilton MLSTARlet enable complex multistep synthesis, graphical user interfaces (GUIs) can be programmed for non-experts. This empowers users to utilize the software and automation with little programming experience and enables access to highly advanced polymer chemistry with only a few hours of training required to run the instrumentation.

The seminal works of Schubert, Hoogenboom, Guerrero-Sanchez, and others along with the prevalence of open-air polymerization techniques influenced our group to combine these two aspects in a manner that is inclusive of post-polymerization modifications. We believe that these developments can be expanded in polymer science, biomaterials, and drug delivery applications. Automation applications in these various fields and air-tolerant polymerization techniques will be further explored in Section 4 [10, 15, 24].

3.1.1. Comparison of Liquid Handling Robotics—In this section, we will present some key differences between various automated liquid handling technologies. Each instrument has unique capabilities that may suited for a particular end user or application. For instance, the Chemspeed Accelerator SLT100 [114–117], Chemspeed ASW2000 [114, 118], Symyx instrument [45], and Freeslate ScPPR [15] are systems that have been utilized to conduct polymer chemistry and are more geared towards the non-programmer. The Chemspeed models have been used for automated RAFT, ATRP, and NMP in parallel reaction vessels with the ability to sample for kinetics experiments, while the Freeslate ScPPR has been used for parallel RAFT reactions [15, 114–117].

Some customizable liquid handling robots can execute advanced experimental protocols that may involve physical movement and manipulation of labware include the Chemspeed SWING, Tecan Freedom EVO, and Hamilton Microlab systems. Meanwhile, the Thermo Scientific Matrix PlateMate 2X3, Andrew Alliance Andrew+, Integra Biosciences VIAFLO 96/384, Rainin BenchSmart96, and Opentrons OT-2 are manageable systems for the non-programmer with the ability to add reagents, complete plate-to-plate transfers, and create a dilution series. For more delicate reactions, many of these instruments can accommodate a glovebox setup containing inert gas lines [97]. Some liquid handling robotic systems, such as those from Unchained Laboratories and Symyx, can also dispense solid materials for reagent preparation and sample handling [95]. A comparison of various attributes (expertise, features, compatibility, integration, and drawbacks) of several liquid handling robots is provided in Table 1.

There are many options available to laboratories in academia and industry and important selection criteria should include programmability, required expertise, throughput potential, and ability to integrate with additional instruments. Strategic and thoughtful implementation of liquid handling robotics can be beneficial for laboratories that conduct research in drug formulation, drug delivery, biomaterials, the life sciences, and more.

3.1.2. Comparison of Powder Dispensing Robotics—In this section, we primarily summarize an assessment of commonly employed powder dispensing instruments which was completed through collaboration between pharmaceutical industry groups from Merck, GlaxoSmithKline, Pfizer, AstraZeneca, and Bristol-Myers Squibb [95].

The various powder dispensing instruments studied include the Chemspeed SWING, Mettler-Toledo Quantos QB5, Unchained Laboratories Freeslate, and Unchained Laboratories Junior. Other instruments that are similar but not covered in this section are the Mettler-Toledo QX96, Chemspeed SDU, GDU-P FD, and J-Kem Eclipse. For a more detailed review of this topic, several reviews are available [96, 97, 134]. These instruments are often operated in the pharmaceutical industry to formulate active pharmaceutical ingredients (APIs). Lower density solids such as L-proline and thiamine HC1 dispense more accurately compared to higher density and inorganic solids such as D-mannitol and NaCl. Some polymers such as polyvinylpolypyrrolidone (PVPP) can be dispensed accurately as well. Many instruments lack the precision to dispense low mass solids. For example, a 2 mg solid mass had up to a 680% and 1700% higher relative standard deviation compared to 10 mg and 50 mg targets, respectively [95]. The practicality of automated solid material dispensing is dependent on the solid's tendency to adhere to a container and density. Instrument accuracy, precision, and ability to perform high throughput experiments can greatly contrast so it is crucial for researchers to understand and evaluate an instrument before committing it to handle solids.

Lastly, the capacity of each instrument to dispense solids accurately and precisely for automated high throughput experiments was determined [95]. The Chemspeed® SWING was found to be the most time efficient and handled dense powders most precisely, but it often experienced technical difficulties which required outside intervention and prevented it from being used in an unsupervised manner. The Quantos QB5 had relatively high precision and accuracy, but it is not compatible with 96-well plates. Meanwhile, the two Unchained Laboratories instruments had a reasonable accuracy and precision, are compatible with 96-well plates, and have a developed data reporting structure that ensures data integrity and fast data transfer. However, this instrument requires more optimization by an experienced user because of performance differences with the two dispense heads and environments (glovebox vs. benchtop).

Overall, each powder dispensing instrument has its own benefits and drawbacks, meaning that selecting the optimal powder dispensing instrument will depend on the nature of the work, type of sample material, and experience of laboratory personnel. The applicability of this instrumentation may vary in the polymer chemistry and biomaterials community depending on the ease of handling the material of interest and level of throughput required.

3.1.3. Analytical Instrumentation—While critical developments have been made in automated sample handling equipment, it is equally important that rapid characterization can also be performed such that various chemical, structural, and dynamic traits can be quantified. For polymers, this includes features such as molecular weight, $Đ$, compositional drift, purity, compactness, flexibility, T_g, crystallinity, mechanical strength, viscosity, Flory-Huggins interaction parameter (χ), conjugation or crosslinking efficiency, and degradation [135]. Despite the large diversity of structural information that can be obtained for polymers and bioactive polymers, several researchers take advantage of chromatography techniques. In polymers and biomaterials work, size exclusion-multi-angle light scattering (SEC-MALS), high-performance liquid chromatography (HPLC), and ultra-performance liquid chromatography (UPLC) are typically used, while gas chromatography (GC) and supercritical fluid chromatography (SFC) are less common [136].

The development of high throughput analytical tools mirrored that of automated synthetic platforms. With the emergence of HPLC in the 1940s, users were required to manually inject samples which made characterization unnecessarily laborious. As high throughput systems developed, autosamplers were incorporated into chromatography instruments in the 1980s. This facilitated less instrument supervision as sample sequences could be implemented. In the 1990s, column switching valves became the norm, simplifying and speeding up the process of experimental optimization [136, 137]. More recently throughout the 21st century, manufacturers have modified stationary phases which has improved all aspects of an experiment such as accuracy, precision, efficiency, and column robustness. Because of these enhanced stationary phases, it is now possible to use smaller, high throughput columns to obtain similar data quality with reduced run time and complete multiple injections in a single experimental run (MISER) [136].

Depending on the quality of the system being used and the diversity of polymers being studied, optimization can be demanding and require advanced expertise. This is due to the numerous parameters that can potentially be varied – mobile phase pH, mobile phase salt concentration, choice of mobile and stationary phase, column dimensions, temperature, backpressure, flow rate, solvent ratios, and the gradient slope. With all these routes of optimization, there is an increasing focus on boosting time efficiency of chromatography experiments. Early on in 2006, a microfluidic system containing 8 channels and 16 solvent reservoirs was developed to compare 8 columns in less than 30 min [136, 138]. While impressive, this highly complicated setup does not provide a way to account for differences in backpressure between the various channels which influences performance. Instead, UPLC systems that can accommodate columns as small as 1 cm in length with fast run times of less than 1 min have become more prevalent [136]. The trends over the past three decades of decreasing column size, particle size, and runtime is also illustrated (Fig. 5).

Chromatography software development was necessary to keep pace with these physical instrument refinements. This has been accomplished in two areas, experimental design and simulations. To streamline method optimization and automated data analysis, software such as ChromSword® Auto, ACD/Autochrom™, and Fusion AE™ have come to fruition. Virscidian Analytical Studio is another software that eases data analysis and reporting through data exporting [112]. Waters Empower™ can complete automated data analysis and

has a structure to track data for integrity purposes. Simulation and modeling software have been utilized for mostly reversed phase chromatography as a way of determining initial optimization conditions (e.g. mobile phase, gradient, and temperature). Examples include ACD/Labs LC-Simulator™, Chromsword®, and ACD/Labs ChromGenius. Typically, parameters such as pKa, logP, logD, and solubility are input for the sample of interest to obtain a "robustness range" for each experimental parameter. This functionality is crucial in ascertaining experimental+ feasibility in a quality by design (QbD) approach [136].

Differential scanning calorimetry (DSC) and transmission X-ray diffraction (XRD) are additional techniques that can be leveraged to determine polymer thermal stability and API crystallinity in the drug delivery and formulation space. DSC can be utilized to measure thermal stability through T_g. While DSC is typically labor intensive, the Malvern MicroCal VP-Capillary DSC and TA Instruments Discovery DSC coupled with an auto sampler enable relatively rapid experimental run times of as many as 24 experiments/day with no user intervention. The Malvern MicroCal VP-Capillary DSC can complete solution measurements through reference subtracting in 96-well plate format [139]. Sample preparation for solid stability DSC measurements can be a major bottleneck, however [140]. High throughput transmission XRD is also possible with the Bruker D8 DISCOVER HTS which can be used to determine amorphous to crystalline form conversion of formulated APIs in well-plate format [141, 142].

To fully characterize bioactive polymers that may contain biomolecules, some additional techniques can be explored. This includes dynamic light scattering (DLS), circular dichroism (CD), surface plasmon resonance (SPR), enzyme-linked immunosorbent assay (ELISA), SAXS, small-angle neutron scattering (SANS), NMR, and cryogenic electron microscopy (cryo-EM). By DLS, the translational diffusion coefficient and thus hydrodynamic size of macromolecules can be quantified. Because of the large number of samples that can be analyzed in a polymer library along with hydrodynamic size dependence on buffer conditions and concentration, the Wyatt Dynapro DLS Plate Reader may provide a solution [135, 143, 144]. CD can be used to study the polymer-protein interface and verify the presence of secondary (190-250 nm) or tertiary (250-350 nm) structures of conjugated biomolecules [135, 145]. SPR and ELISA can validate binding of biomolecules but also screen the binding affinities of various bioactive polymers in a large library. The Cytiva (formerly GE Healthcare Lifesciences) Biacore 8K+ can screen up to 2300 molecules/day directly in 384-well plates and run unattended for 72 hours [135]. For downstream cell testing, high throughput pipettors such as the Integra Biosciences VIAFLO 96/384, Integra Biosciences ASSIST PLUS liquid handling robot, and Rainin Liquidator™ 96 can accomplish cell seeding into 96- or 384-well plates, serial dilutions, and reagent addition.

Various characterization tools are available for both polymers and bioactive polymers and can be incorporated into a high throughput experimental workflow. For characterizing polymers, chromatography techniques such as gel permeation chromatography (GPC)/SEC, HPLC, and UPLC are commonly used and have been developed over the years to manage high throughput experiments. Smaller column dimensions and smaller resin particle size have enabled rapid run times. DSC and transmission XRD which can be utilized to characterize polymers and APIs, respectively, can be conducted in well-plate format

resulting in greater efficiency. Lastly, structural traits of polymers and biomacromolecules along with binding affinity can be characterized by an array of techniques: DLS, SAXS, SANS, CD, and SPR. High throughput characterization is crucial, as it provides researchers with the ability to obtain data in a rapid fashion to then be interpreted by traditional analytical tools or data-driven design algorithms.

3.2. Artificial Intelligence, Machine Learning, and Simulation

While the adoption of robotic instrumentation in research has enabled HTS in chemical research and development, brute-force HTS approaches typically remain cost intensive and inefficient. Even with well-designed protocols, resulting hypotheses of molecular design principles from HTS may be incomplete or poorly understood. For polymers and other soft materials, these limitations can be exacerbated due to challenges associated with synthesis or characterization, as discussed in previous sections, in addition to inherent complexity and hierarchical origin of the material properties [146, 147]. Traditionally, computational and/or theoretical tools might be applied to bridge the gap between experimental observations and their mechanistic origins [148]. However, AI and ML, perhaps integrated with theory and simulation, are playing ever more important roles in polymer-based biomaterials and therapeutics. In this section, we highlight recent developments in AI, ML, and modeling with relevance towards designing polymer-based materials; some specific applications of these techniques are discussed in Section 4.5.

3.2.1. Emergence and Role of Databases—While the development and adoption of automated workflows promises to accelerate data generation, the ultimate utility of that data, beyond the initial use case for its generation, may depend on successful integration into accessible, searchable databases. For hard materials and small molecules, the growth and utilization of databases (e.g. the Materials Project, https://materialsproject.org; the Harvard Clean Energy Project, http://cleanenergy.molecularspace.org; and the Computational Materials Repository, https://cmr.fysik.dtu.dk) have enabled virtual screening and design in application areas such as organic photovoltaics, piezoelectrics, and Li-ion batteries [149]. By comparison, efforts to effectively develop and utilize databases in the realm of soft materials are both fewer in number and less mature in application. Some notable examples include Chemical Retrieval on the Web (polymerdatabase.com), the Polymer Genome (polymergenome.org), Polymer Property Predictor and Database (pppdb.uchicago.edu), and PoLyInfo (https://polymer.nims.go.jp/en/). Such databases may provide specific thermophysical properties for a particular polymer or even offer functionality to predict properties for inputted chemical structures. Nonetheless, the formats and navigational features of such databases are not well suited for ML, and it remains an open question as to whether they should and to what end?

Well-known challenges for soft materials databases include the qualitative diversification of soft materials systems and the contextual dependence of emergent properties [146, 147]. To what extent is a compilation of thermophysical properties of homopolymer melts informative for the design of heterogenous biomaterials and polymer therapeutics? Often, the properties of interest, computational or experimental, will be specific to the application area. These challenges are likely to be resolved incrementally, perhaps resulting in a

combination of both more specific (e.g. the solubilities of protein-polymer conjugates) and more general databases (e.g. libraries of quantum chemistry calculations for monomeric units).

Irrespective of the application, effective representation and searchability of data will be desirable. Many of the same features that make polymers attractive design platforms, such as tunability with respect to composition, architecture, and molecular weight—also present challenges for cataloging data, since simple simplified molecular-input line-entry system (SMILES) strings or typical nomenclature will fail to adequately describe the system. Some notable examples to build or expand online notations to describe polymers include SYBYL Line Notation (SLN) [150], Hierarchical Editing Language for Macromolecules (HELM) [151], CurlySMILES [152], and BigSMILES [153]. Representations through HELM may be attractive for applications involving polymer therapeutics, since the hierarchical nature enables description of complex biomolecules and conjugates, while BigSMILES accounts for the stochastic nature of some polymer structures. In any case, additional refinement, and importantly, routine adoption of these representations will be required for widespread data dissemination.

3.2.2. Utility of Machine Learning Techniques—Despite limitations in data availability, AI and ML techniques, in various forms, have long been used to analyze and predict the properties of polymer-based materials. Historically, chemists and medical scientists have relied on intuition and experience to select chemical pathways and establish hypotheses about materials properties and activity, which can bias results towards preferred chemistries or predisposed model interpretations [154, 155]. Without guidance beyond human intuition, it can be difficult to navigate a complex design space involving choices regarding monomer chemistry, DP, architecture, sequence, composition, etc. – all of which may be critically important to a particular property or figure of merit. Depending on the nature of the data, ML techniques, often either supervised or unsupervised, can provide guidance in soft materials design. In supervised ML, both inputs and outputs are known across the dataset, whereas inputs are known but the outputs are left undefined for unsupervised ML. Both approaches have been applied effectively in biological sciences and engineering, and the utility of these ML approaches in the realm of polymer chemistry is illustrated **(**Fig. 6).

Unsupervised ML algorithms typically take the form of dimensionality reduction or clustering techniques for analyzing data. Dimensionality reduction techniques, such as principal component analysis (PCA), independent component analysis (ICA), and diffusion maps (dMaps) seek to identify a low-dimensional parameterization of a high-dimensional dataset, akin to feature extraction or pattern recognition. Such techniques have helped to identify protein-folding pathways [156, 157] and key attributes in polymer precipitation inhibitors in drug formulations [158]. Recent work by Green et al [159] also demonstrated the potential of unsupervised ML in using PCA to elucidate the structure-function relationships in transfection, uptake, and cell viability in a combinatorial library of PBAEs used for gene delivery. Meanwhile, clustering techniques, such as k-means, fuzzy C-means, and agglomerative hierarchical clustering seek to organize or process data into groups that exhibit similar characteristics; these techniques may be useful for compound selection in

drug discovery and HTS applications [160]. A notable application of clustering is in the analysis of gene expression data to understand and manipulate cellular regulatory networks [161].

Supervised ML which could function in tandem with insights provided by unsupervised ML, further enables construction of predictive models to interrogate the chemical relationships underlying physiochemical polymer properties [162]. Using techniques such as random forests (RFs), support vector machines (SVMs), Gaussian processes (GPs), and neural networks (ANNs), models can be trained to find specific relationships between labeled output data and input features or descriptors of a system, such as chemical fingerprints. Consequently, supervised ML is being actively explored to predict polymer properties based on structure and composition [148, 154, 162–170]. For material discovery, quickly and effectively learning from iterative test cycles is especially critical [34, 171]. Feedback-driven QSPR model adaptation to newly obtained activity data and multiple round screening through iterative feedback has shown to lead to significantly better outcomes than single large batch screens [172, 173]. Realizing this, a subset of ML methods known as active learning has recently been adopted to maximize the efficiency of learning from data generated in real time. Active learning methods assist in the selection process by considering both domains of the chemical space that have high and low amounts of information available. In doing so, active learning algorithms “exploit” known information in the QSPR model to suggest compounds with a high probability of exhibiting properties of interest. These suggestions can also add information in spaces of low chemical information [166, 171].

3.2.3. Simulation and Modeling—Traditionally, the role of modeling and simulation in materials discovery has been the development of insights or design principles based on detailed mechanistic investigation. However, the coupling of phenomena over a vast range of spatiotemporal scales presents technical challenges for simulating polymer-based systems, which necessitate the use of specific techniques that are targeted to address properties at a particular resolution. For example, quantum chemistry or electronic structure calculations are somewhat limited in application [174] since the computational expense of such methods limits the description of systems to monomer units or perhaps small oligomers. More commonly, polymer-based systems are studied using some form of Monte Carlo (MC) or Molecular Dynamics (MD) techniques [175] at a resolution that makes calculating a given property or figure of merit computationally tractable. While MD numerically integrates (typically) classical equations of motion to produce a sequence of polymer system configurations, MC produces configurations through a stochastic move proposal process, which is not necessarily constrained by physical laws. MD thus permits examination of both dynamical and statistical properties, while MC is limited to interrogating the latter. Although MC may have an advantage over MD in terms of efficiency for certain representations of polymer systems (e.g. lattice models), MD is overall more common due to its versatility and relative ease of application.

Whatever the chosen simulation methodology, there is significant interest in using simulation in materials discovery. Since the computational cost associated with simulating new polymer systems is typically less than the material and labor cost of synthesizing and

characterizing new polymers, simulations can provide useful information in two forms. First, simulations can provide access to additional properties, microstructural characteristics, or molecular descriptors that are not accessible by experimentation, which may be useful in the construction of more efficacious QSPRs. Second, since the computational cost associated with new polymer compositions is typically less than the materials and labor cost of synthesizing and characterizing new polymers, simulations may also significantly expand exploration of chemical space. An emerging direction is to leverage simulated or computed properties in data-scarce regimes via transfer learning [176], a strategy now being explored for drug discovery [177].

In recent years, there has been a growing emphasis on developing high throughput modeling strategies [178] that can take advantage of emerging data-centric design methodologies. Virtual screening approaches related to structure prediction or ligand binding have long been a part of small-molecule drug discovery [179, 180]; however, the conformational heterogeneity and overall complexity of polymer systems limits the application of similar approaches. Alternatively, tailored systematic screening methods that use simulation to rapidly generate target system properties can be developed [168, 169, 181]. Although atomistic resolution simulations are likely to be too computationally expensive for many applications, so-called coarse-grained (CG) simulations, which reduce the degrees of freedom present in a simulation by grouping multiple atoms or functional groups together into combined interaction sites [175], can make certain calculations more tractable.

For biomaterials design, an important facet of CG simulations is whether the CG models reflect specific materials chemistry. Often, CG simulations of polymeric systems may utilize generic models that describe classes of materials, rather than particular chemistries; the results of such simulations may still be useful in biomaterials discovery by providing general guidance towards desirable conditions, properties, or topologies to achieve a target function. However, CG models may also be developed in the context of a specific system. In some cases, pre-parameterized models such as the MARTINI force field for biomolecular systems [182, 183] may be available for describing the desired chemical space. Otherwise, CG models will need to be developed based on atomistic simulations or experimental measurements; the development of methods for defining and parameterizing coarse-grained model is an active area of research [184–191]. Nonetheless, the construction of CG models can be non-trivial and require significant human intervention and guidance [190]. Therefore, algorithms and software to automate CG mapping [189–192] and parameterization [187, 188] are of significant interest for applications targeting high throughput simulation and integration with AI and ML techniques [182, 183].

3.2.4. Optimization—The utilization of optimization techniques is also an important consideration for leveraging QSPR models for problems in materials design [193, 194]. Given the vast number of design variables for polymers considered as potential biomaterials or therapeutics, coupling an optimization algorithm to a viable QSPR model enables efficient exploration of design space and rapid identification of candidate materials.

Traditional optimization problems are often approached using gradient-based techniques, such as the steepest-descent, conjugate-gradient, or Broyden-Fletcher-Goldfarb-Shanno

(BFGS) methods. A limitation of gradient-based methods is the need for a continuous vector space, upon which gradients can be constructed; this can be problematic since the design space over molecular chemistry, let alone polymer chemistry, is both large and discrete. Gómez-Bombarelli et al. demonstrated a resolution to this issue by employing auto-encoders to transform discrete chemical structures (as SMILES strings) into continuous vector spaces that would further function as inputs for property prediction [195]; using this approach, gradient-based optimization enabled efficient identification of functional drug-like molecules. Although their application was limited to molecules with fewer than nine heavy atoms, extensions and modifications should enable similar creative approaches in the space of polymer design.

Several gradient-free optimization techniques, including particle swarm optimization [196], various evolutionary strategies [193], and Bayesian optimization (BO) techniques [197] are also popular approaches that have been used in soft materials design. With these techniques, it may not be necessary to transform chemical structures into a latent vector space, although that may still be desirable. Implementation of BO frameworks is increasingly popular with data-driven design paradigms, since existing datasets can be leveraged to form reasonable starting points for Bayesian inference. BO in tandem with the supervised ML technique of GP regression is a powerful combination for both efficient dataset construction via active learning and design.

4. Applications of Automation and Data-Driven Design

This section will focus on applications related to automation and data-driven design approaches to polymer synthesis, antimicrobial polymers, biodegradable polymers for gene delivery, polymers for oral drug delivery, and drug discovery. Automation and data-driven design have been introduced into biomaterials and drug delivery research, and we believe that the growth of these concepts will only accelerate.

4.1. Antimicrobial Polymers

Here, we describe the application of combinatorial and high throughput polymer chemistry in the realm of antimicrobial polymers. This area of research is exploratory and thus benefits from a combinatorial approach to potentially reveal QSPRs. As observed from numerous examples presented in this review, a combinatorial and high throughput polymer synthesis approach has accelerated research progress and has uncovered some major findings.

Resulting from widespread antibiotic usage to treat infections, there is a gradually increasing number of multidrug resistant bacteria, which is a major global health problem [198–201]. This predicament is only exacerbated by the fact that a new class of antibiotics has not been discovered in over 30 years [202]. In fact, it is projected that multi-drug resistance may cause 10 million deaths by 2050 [203]. Similar to antimicrobial peptides (AMPs), antimicrobial polymers are being developed to contain cationic monomers that interact with the negatively charged bacterial cell membrane surface and hydrophobic monomers to infiltrate the lipid membrane interior. With the advent of more robust and efficient synthetic approaches, the main challenge is to strike a balance between charge and hydrophobicity such that polymers harm bacterial over mammalian cells [203, 204]. As illustrated in this

section, an efficient process for identifying these polymers can involve combinatorial and high throughput polymer synthesis.

Boyer and Wong led an effort to accomplish this in planktonic and biofilm bacteria associated with the gram-negative strain *Pseudomonas aeruginosa* [203]. A small library of random heteropolymers was synthesized by RAFT containing cationic monomers *tert*-butyl (2-acrylamidoethyl) carbamate (Boc-AEAm) and *tert*-butyl (4-acrylamidobutyl) carbamate, along with hydrophobic monomers isoamyl acrylate, 2-phenylethyl acrylate, and 4-(pyren-1-yl) butyl acrylate. By quantifying minimum inhibitory concentration (MIC), hemolytic activity, and bactericidal activity, it was found that cationic and hydrophobic monomers were necessary to cause bacterial cell death in a specific manner. A further examination of potential polymer compositions was required to begin establishing a QSPR.

This came in a collection of follow-up studies also from Boyer, Wong, and co-workers in which PET-RAFT was applied. First, 32 complex quasi-block copolymers were synthesized containing fixed mol% of hydrophobic, hydrophilic, and cationic monomers at DP = 20, 40, and 100 [205]. MICs for gram-negative and gram-positive bacteria along with hemolytic activity was quantified to understand the specificity of each polymer (Fig. 7). It was found that polymer DP and block organization tuned activity against specific bacterial strains while composition of hydrophilic and hydrophobic monomers in local blocks affected specificity. In the subsequent set of experiments, a library of 120 polymers was synthesized by PET-RAFT at a fixed DP = 40 containing cationic, hydrophilic, and hydrophobic monomers [206]. Three groups of cationic monomers were selected with primary, tertiary, or quaternary amines. An MIC screen was done for each using gram-positive (*Staphylococcus aureus*), gram-negative (*Pseudomonas aeruginosa*), and mycobacteria (*Mycobacterium smegmatis*) strains. Differences in activity related to the presence of cationic monomer type were observed. Polymers containing primary amines were most effective against gram-negative bacteria while compositions with quaternary amines were most effective against gram-positive and mycobacteria. For all strains, an MIC of 32-64 μg/mL was achievable. Overall, this work illustrates the potential of utilizing a high throughput screening workflow to uncover the importance of monomer composition. More recently in the space of antimicrobial polymers, it was revealed that slug flow polymerization by PET-RAFT in a flow reactor can yield over 27 g/day of polymer that can be used for downstream applications [207].

Additional design considerations were considered by others, namely the effect of multivalent display of antimicrobial polymer and incorporation of sugar-derived monomers. Rather than focusing efforts on linear polymers for these experiments, Gibson and others aimed to understand the effect of multivalent display of polymers [208]. They created a library of 50 gold nanoparticles functionalized with polymers synthesized by RAFT containing varying valency of cationic monomer dimethylaminoethyl methacrylate (DMAEMA) relative to hydrophilic monomer *N*-hydroxyethyl acrylamide (HEAm) whereby both polymers were synthesized at DP = 10, 25, 50, and 100. Multivalent display of polymer exhibited about two- and eight-fold improvements in activity against mycobacteria and gram-negative *Escherichia coli*. Because of the presence of carbohydrate receptors on the surface of bacterial membranes, Zheng et al synthesized a library of over 25 polymers containing

cationic *N*-[3-(dimethylamino)propyl] methacrylamide (DMAPMA), hydrophobic *N,N*-diethylmethacrylamide (DEMAA), and sugar-containing 2-(methacrylamido) glucopyranose (MAG) by recyclable-catalyst-aided, opened-to-air, and sunlight-photolyzed RAFT (ROS-RAFT) [209, 210]. Through this approach, they concluded that polymers with the greatest antimicrobial activity had high incorporation of MAG and DEMAA despite low presence of cationic monomer [210].

Progress has been made towards automation in the space of antimicrobial polymers. Since successful antimicrobial polymer candidates are typically screened based on biological activity, it is beneficial to synthesize and prepare polymers directly in 96-well plates. Gibson and others were able to apply these principles of high throughput polymer chemistry for antimicrobial purposes [24]. Taking advantage of the automated Gilson Pipetmax 268 liquid handling robot and an oxygen-tolerant photo-RAFT technique that uses trithiocarbonate photoredox catalysts [24, 211], 108 polymers were rapidly synthesized in 96-well plates. DMAEMA was the cationic monomer randomly copolymerized to varying degrees with hydrophilic or hydrophobic monomers. It was found that a copolymer containing poly(propylene glycol) methacrylate (PPGMA) displayed a 16-fold improvement in bioactivity by MIC compared to DMAEMA homopolymer (Fig. 8). The authors remarked that PPGMA was not the most hydrophilic or hydrophobic monomer, indicating that there is likely data nonlinearity present. This implies that data interpretation of these biological assays is not intuitive, and that data-driven design may be well-suited for high throughput experimentation.

For the early-stage research associated with antimicrobial polymer identification, combinatorial chemistry and high throughput polymer synthesis in conjunction with initial polymer rational design have been crucial tools to speed up progress. Selecting design criteria of interest can be challenging, however, given the wide range of possibilities and limited time and material resources. Also, as referenced by Gibson et al., data sets can be nonlinear, meaning it is nearly impossible for researchers to interpret and form important decisions. As a result, further development of high throughput tools and the advent of data-driven design approaches in antimicrobial polymer discovery will push the limits of research in this field.

4.2. Biodegradable Polymers for Gene Delivery

In this section, we will review research related to polymers utilized as gene delivery vehicles. Because these examples involve complexation of polymers and DNA, all of the polymers described are biodegradable. A combinatorial, high throughput approach is commonly utilized by researchers in this field to identify a specific cationic polymer or set of conditions (e.g. concentration or buffer type) required to maximize gene delivery efficiency while maintaining sufficient cell viability. While this field has been established for over a decade, high throughput approaches have mainly been utilized for the purpose of polymer HTS in a semi-automated fashion. Because of this, there is a massive opportunity for high throughput, automation, and data-driven design of polymers to impact gene delivery research.

Nucleic acids which are high molecular weight, anionic, and hydrophilic are not naturally equipped to permeate the cell membrane and have low bioavailability. In addition, these biomolecules are vulnerable to nuclease activity [212–214]. As a result, DNA and RNA therapeutics are challenging to deliver to cells, necessitating the use of an efficient delivery vehicle. While there are toxicity and manufacturing concerns associated with viral vectors, polymeric gene delivery has emerged as a viable strategy [110]. Some common gene delivery strategies include polyelectrolyte-nucleic acid complexes [213, 214] and grafting-to polymer bioconjugation [21, 212]. In this section, the focus will be on degradable cationic polymers because this class of macromolecules has been most extensively utilized in HTE and HTS related to gene delivery.

As described in Section 2.4, Anderson, Langer, and co-workers provided an impetus to implementing a high throughput approach in polymeric gene delivery [110, 111]. Green, Langer, Anderson, and co-workers demonstrated that a combinatorial polymer synthesis approach could yield candidates for gene delivery with similar effectiveness as viral vectors [215]. They designed a combinatorial library of 36 PBAE polymers which were derived from 3 diacrylates modified with 12 diamines. In primary human umbilical vein endothelial cells (HUVECs), transfection efficiency of promising polymer candidates was similar to that of adenovirus while outperforming that of standard polymer vehicle polyethylenimine (PEI) by about two times. In a more expansive study, PBAEs were prepared by addition of amines to diacrylates using a library of 129 amines and diacrylates [216]. Through a high throughput synthesis, characterization, and screening for gene delivery capability, a structure-activity relationship was uncovered. Characteristics found to maximize gene delivery efficiency of eGFP in COS-7 cells included the presence of hydroxyl side groups, primary amine polymer end groups, small diameter (< 200 nm), and about neutral zeta potential. Similar to previous work, polymers were identified that had similar efficiency as an adenovirus vector and greater efficacy compared to standard polymers PEI and Lipofectamine 2000.

Wilson, Green, and co-workers have further explored the effect of polymer architecture on plasmid gene delivery [217]. Initial work with biodegradable PBAEs focused on linear polymers, so branched poly(ester amine) quadpolymers (BEAQs) were designed by various combinations of diacrylate, triacrylate, and amino entities such that the degree of branching correlates with the presence of triacrylates. Various properties of BEAQs, linear polymers, and standard polymers (PEI, JetPRIME, and Liopfectamine 2000) were characterized by DNA binding assays, DLS, electrophoretic light scattering (ELS), transmission electron microscopy (TEM), transfection studies, and cell uptake assays. This combinatorial approach enabled an extensive examination of transfection efficacy, expression, and viability due to degree of branching and polymer concentration (Fig. 9). Ultimately, BEAQs displayed enhanced transfection efficacy of eGFP to HEK293T and ARPE-19 cells over linear PBAEs and standard polymers while maintaining solubility in high serum conditions.

In a similar manner, Yan and Zhu et al synthesized and screened a library of 126 degradable, cationic poly(alkylene maleate mercaptamine)s (PAMAs) [218]. PAMAs were synthesized via maleate-thiol Michael addition of 7 poly(alkyl maleate)s (PAMs) and 18 mercaptamines. Testing the effect of backbone or side group functionality on polymer-nucleic acid solubility,

gene delivery efficiency, and DNA binding yielded a group of candidates. The leading polymer was complexed with plasmid DNA of TNF-related apoptosis-inducing ligand (TRAIL) in an *in vivo* mouse model, exhibiting a 93% tumor inhibition rate. This represents approximately six-fold improvement in potency relative to standard PEI-based gene delivery. Once optimal candidates are identified, it is possible to take a finer approach, such as analyzing subcellular structures to determine mechanism of action.

The field of gene delivery can benefit significantly with an automated and high throughput approach. Mishra and Wilson et al. have taken a major step in this direction by demonstrating the utility of an HTS workflow in identifying biodegradable polymers and transfection conditions to deliver plasmid DNA into difficult-to-transfect human retinal pigment endothelial (RPE) cells with high efficiency and minimal cytotoxicity. A library of 140 polymers were prepared to package mCherry and nuclear GFP plasmids. Additions, transfer of nanoparticles, and media changes were completed using the semi-automated VIAFLO 96/384. The Thermo Scientific Cellomics VTI executed an automated image collection and analysis protocol to obtain rapid evidence of cell transfection efficacy and viability [30]. As described previously, the ability to synthesize polymers in 96-well plates in solvent such as DMSO which is tolerable to cells at low concentration can result in streamlined experimentation that can be automated. Polymer viscosity can impact data quality and the ability to automate so this may need to be monitored [110].

Through this review of biodegradable polymers for gene delivery, it can be observed that combinatorial, high throughput, and semi-automated methods are in use to identify cationic polymers that efficiently delivery plasmid DNA with minimal cytotoxicity. Since the biological screening process typically involves 96-well plates, it is amenable to automation. Some degree of user observation, however, may be required to prevent the inclusion of highly viscous polymers that can obfuscate results. Lastly, data-driven design strategies would significantly improve polymer design and additional iterations while speeding up experimentation time.

4.3. Polymers for Oral Drug Delivery

Oral drug delivery is another area in which there is the potential to employ automation and data-driven design techniques as they relate to identifying polymer excipients for hydrophobic drugs. In this space, combinatorial approaches are often leveraged with one recent instance of automation being exploited to advance polymer synthesis and HTS. Data-driven design of polymers has not been widely introduced to this research field, so there are several unexplored avenues for further progress. In this section, we will focus on applications related to oral drug delivery as this is the most prevalent route of administration [8].

About 40% of approved drugs are classified as having low solubility compared to 90% of drugs that are in the pipeline. Rapid crystallization of poorly soluble drugs results in low bioavailability as drug is unable to traverse the gastrointestinal tract. Amorphous solid dispersions (ASDs) are typically created to formulate the drug, also referred to as the API, promoting polymer-drug non-covalent interactions (e.g. hydrogen bonding) (Fig. 10) [219]. These polymer-drug interactions present a more favorable free energy state and thus prevent

API crystallization to achieve supersaturation [8, 220]. This crystallinity can be determined to varying extents by DSC, transmission XRD, and polarized light microscopy while Fourier-transform infrared (FTIR) and Raman spectroscopy can confirm polymer-drug interactions. In addition, various modeling approaches can be adopted to verify the likelihood of hydrogen bonding or interaction with water molecules [220–224]. Despite the vast chemical space of API moieties, cellulose-based polymers, such as hydroxypropyl methylcellulose acetate succinate (HPMCAS), and poly(vinylpyrrolidone) (PVP)-based polymers are overwhelmingly utilized in the oral drug delivery community [8, 219]. This is counterintuitive given that APIs are often identified by HTS and data-driven design approaches, but the same level of complexity does not exist for polymer excipients that are crucial in stabilizing these small molecules.

Numerous researchers have an objective of improving our understanding of polymer excipient design based on the functional groups present on the hydrophobic API of interest. Matzger and others studied the effect of functional groups (alkyl, ketone, and hydroxyl) that can cause polymer heteronucleation or crystallization of APIs pyrazinamide and hydrochlorothiazide. Side group functionalities were introduced via post-polymerization modification which was useful in isolating the effect of individual side groups on crystallization inhibition and polymer heteronucleation [225]. Reineke and others synthesized a small library of diblock terpolymers by RAFT to create spray dried dispersions (SDDs) with the hydrophobic API probucol at 10 and 25 wt% API. The first block consisted of poly(ethylene-*alt*-propylene) (PEP), *N*-isopropylacrylamide (NIPAM), or *N,N*-diethylaminoethyl methacrylate (DEAEMA), while the second block contained both *N,N*-diethylmethacrylamide (DMA) and 2-methacrylamidotrehalose (MAT). By DSC, the presence of amine functionality for hydrogen bonding correlated to lower crystallization levels. Dissolution testing also revealed solubility is maximized in acidic conditions (pH 3.1). This combinatorial approach utilizing copolymers enabled efficient identification of important structural traits of designer polymer excipients [226]. Hillmyer and co-workers analyzed the effect of polymer end groups and molecular weight by utilizing 10 RAFT CTAs in synthesizing a 17-polymer library of various PNIPAMs which were used to form SDDs with phenytoin at 10 wt% drug loading. They found that the highest performing polymers inhibited crystallization of the API phenytoin for about 6 hours while exhibiting almost 20-fold improvement in dissolution compared to API alone. Through this combinatorial approach, they identified that lower molecular weight PNIPAM and those containing a longer flexible alkyl chain tended to form micelles (R_h > 30 nm) and inhibit API crystallization [227].

Similarly, Ting et al. set out to understand the effect of side groups (methoxy, succinoyl, hydroxypropyl, and acetyl) on inhibiting crystallization of APIs probucol, danazol, and phenytoin. These APIs were selected because they had contrasting logP, melting temperature (T_m), crystallization kinetics, and functional groups responsible for crystallization. The effect of each polymer side group was isolated by copolymerizing respective monomers MA, HPA, 2-carboxyethyl acrylate (CEA), and acrylic acid (AA) with HPMCAS by RAFT before preparing SDDs of polymer and drug. FTIR was needed to characterize polymer-drug interactions while polarized light microscopy, HPLC aqueous dissolution experiments, transmission XRD, and DSC were used to classify solubility and crystallinity. Through this

screening, it was found that CEA copolymers maintained supersaturation of the slow crystallizer probucol while HPA performed adequately for faster crystallizers danazol and phenytoin because of the presence of hydroxyl groups to engage in hydrogen bonding with API (Fig. 11) [219]. Johnson et al. also considered a unique approach, creating polymer blends to be used to attain API supersaturation such that the impact of individual monomers can be quantified. They found that blending API with NIPAM and HPMCAS, hydroxypropyl methylcellulose (HPMC), DMA, and HEAm resulted in enhanced supersaturation of phenytoin relative to individual homopolymers. Further characterization suggested that the formation of micellar structures due to the presence of NIPAM may encourage polymer-drug interactions [228].

In oral drug delivery, traditional combinatorial techniques have enabled researchers to quantify the effects of side group moiety, molecular weight, polymer hydrophobicity, and polymer mixtures on ability to supersaturate hydrophobic APIs [219, 225–228]. While fruitful, many of these workflows are throughput-limited and prone to error and variability due to labor intensive polymerizations and manual pipetting. Ting et al. aimed to screen and characterize a library of over 60 polymers to improve solubility of phenytoin, a fast-crystallizing API. The polymer design plan was to synthesize random heteropolymers containing a hydrophilic monomer and a precipitation inhibition monomer at varied incorporation that may hydrogen bond with API. RAFT polymerization was automated with a Freeslate ScPPR which dispensed required volumes of manually prepared monomer, initiator, and CTA in reaction vessels that included nitrogen flow and temperature control. Additionally, precipitation inhibition screening was automated with the Tecan Freedom EVO 200 liquid handling robot as pipetting of polymer and drug as well as preparation of HPLC samples at three time points was rapidly completed. Evaluation of SDDs in biorelevant media and *in vivo* pharmacokinetics showed over 20-fold improvement in area under the dissolution curve compared to API alone [15].

As illustrated by recent work in polymers used for oral drug delivery, defining a clear polymer design paradigm will be key to improve API dissolution and prevent crystallization. It is apparent from these experiments that the goal of achieving supersaturation of poorly soluble drugs is challenging and involves several parameters [226]. Not only is polymer design important to maximize polymer-drug interactions, but also other factors come into play such as drug loading level, conditions for preparing SDDs, dissolution conditions, and more. As a result, establishing QSPRs will likely require some combination of automation and data-driven design. Applying HTE and HTS to this space is an emerging concept [15] with few recent cases of a high throughput or combinatorial approach being utilized.

4.4. Bioactive Polymers

Multivalency plays an important role in biological and synthetic systems. The last two decades of research has seen an explosion in the field of design and delivery of multivalent drugs with importance in drug delivery, glycoscience, immunology, cancer therapy, and regenerative medicine. However, evaluating structure-function relationships for multivalent polymer scaffolds is challenging because of the diverse nature of available physicochemical characteristics. It is known that factors such as polymer scaffold flexibility and ligand

presentation are crucial to maximizing binding interactions of interest [229]. Because the ability to design polymers for this purpose does not currently exist, high throughput study and data-driven approaches could be beneficial in accelerating research progress and identifying useful design strategies. In this section, the focus will be on bioactive polymers in vaccines, glycopolymers, and polymer-peptide conjugates.

In protein-based vaccine development, formulation of small molecule Toll-like receptor agonists (TLRa) leads to greater T cell immunity and antibody response with applications in infectious diseases and cancer. Lynn et al. synthesized hydroxypropyl methacrylamide (HPMA) and NIPAM polymer conjugates in a combinatorial fashion containing two agonists TLR-7/8a to understand the effect of TLRa valency and linker selection on innate immune activation [22]. While these authors found that higher valency leads to greater innate immune response, they also noted that it would be valuable to explore more diverse polymer composition and architecture. Laga and others attempted to increase the complexity of polymer design by synthesizing a library of 13 polymer-TLR-7/8a conjugates containing statistical terpolymers, statistical copolymers, diblock copolymers, multiblock copolymers, and particle-forming statistical co-polymers functionalized by azide-alkyne Huisgen cycloaddition or an acylation reaction [230]. They utilized a large library of monomers such as HPMA, *N*-propargylmethacrylamide (PGMA), and *N*-(2-aminoethyl) methacrylamide hydrochloride (AEMA) with valency ranging from 1-11.7 mol% and molecular weight from about 36 kDa to 121 kDa. As a result of this combinatorial approach, TLR-7/8a conjugates that induced the desired T cell immune response and displayed sufficient potency were identified. Exploring these few parameters of polymer composition and linker alone resulted in a large, diverse chemical space [22, 230, 231]. Incorporating automation and data-driven design would further increase the parameter space that can be studied while ensuring efficient experimentation.

Glycopolymers are also bioactive materials that would benefit from a similar approach. Carbohydrate-protein interactions at the cell surface are crucial for cellular signaling and recognition with importance in the immune response. Lectins are proteins that modulate interactions with glycans and individually have low affinity to glycans in the mM range. By the cluster glycoside effect, a multivalent presentation of glycans enhances the binding affinity of this interaction [232, 233]. Because multivalent monosaccharides have high avidity but low specificity, there is a focus on displaying multiple glycan types and increasing polymer complexity to understand the design parameters necessary for particular interactions. Gibson and co-workers synthesized nine homogenous and heterogenous polymers containing varied mol% of galactose and mannose to determine activity against *Ricinis communis* agglutinin (RCA_{120}) and cholera toxin lectins [232]. By biolayer interferometry (BLI), it was found that specific inhibition of RCA_{120} and cholera toxin was improved with the incorporation of the two glycan types on the same polymer scaffold. The benefit of including additional functional units was supported by previous work [233]. More recently, in the context of infectious disease detection, Richards et al. studied the interaction between hemagglutinins (HAs) and sialoside glycoproteins typically found on the surfaces Influenza A and human cell, respectively [234]. They synthesized HEAm polymers by RAFT, functionalized with galactosamine, and immobilized on the surface of various gold nanoparticles (30, 50, and 70 nm diameter) to study the effect on binding affinity to

Influenza A HAs. In a similar study, Gibson and co-workers also studied 30 formulations of HPMA and HEAm polymers functionalized with galactosamine and grafted on the surface of gold nanoparticles [235]. By BLI, both polymer types performed similarly despite different aggregation behavior. However, this paper highlights that functional molecule presentation and density can affect binding affinity.

Developments in open-air RAFT have already begun to make an impact in this field. The ability to synthesize polymers by PET-RAFT in 96-well plates was a major step in efficiently generating large polymer libraries, making it possible to investigate polymer design parameters. For instance, Gormley, Boyer, Chapman, and co-workers synthesized a polymer library by PET-RAFT with zinc tetraphenylporphyrin (ZnTPP) as a photocatalyst [9]. ZnTPP converts triplet oxygen to singlet oxygen which can then be scavenged by DMSO. A library of linear and star (3-arm and 4-arm) polymers was synthesized at various DPs and functionalized with mannose. A lectin binding assay was then completed to determine that lower DP 3-arm star polymers performed best (Fig. 12). This collection of work in bioactive glycopolymers has highlighted that multivalent presentation of glycans and slight modifications to polymer design and architecture can have implications in binding affinity and activity. Further experimentation by a high throughput, combinatorial, and data-driven design approach would likely result in even more polymer design flexibility and analysis of structure-function.

In a seminal work, Moore and co-workers have recently reported the use of multivalent polymer scaffolds for targeting protein aggregation for the first time [236]. Protein misfolding leads to aggregation resulting in a wide range of diseases including Alzheimer's and Parkinson's. Both diseases are characterized by the formation of highly ordered amyloid fibrils mainly arranged in β-sheets, however, investigating disassembly of these fibrils remains largely unexplored. Moore and others designed multivalent polymer-peptide conjugates that interact with and disassemble amyloid β fibrils *in vitro.* Building on previous work, HPMA was copolymerized with NHS acrylate by RAFT followed by subsequent attachment of peptide via NHS ester chemistry [237]. Five multivalent polymer-conjugates with 7 mol% peptide loading and various molecular weights (22-224 kDa) were chosen to investigate the disassembly effect on preformed $A\beta_{40}$ fibrils. The ability to disassemble fibrils increased with increasing molecular weight. While Moore's group tested a total of 10 polymers, this multivalent strategy can be adopted easily to high throughput screening and data-driven design approaches.

Other recent developments in the field include the fascinating works by Gianneschi and co-workers in which they developed multivalent synthetic scaffolds by organizing functional peptides as dense side chain arrays onto polymeric scaffolds [145, 238–240]. These materials were classified as (1) peptide-polymer amphiphiles (PPAs) and (2) protein-like polymers (PLPs). The design of PPAs was accomplished by synthesizing block copolymers with a dense grouping of peptides as the side chains of the hydrophilic block, connected to a hydrophobic block to yield micelles that retain specific peptide interactions and orientations. PPAs were synthesized using two approaches that involved either conjugation of peptides to a synthesized polymer (graft-to) or by the incorporation of peptides onto a growing polymer chain (graft-through). Synthesis of PPAs via a graft-to approach involved generating diblock

copolymers by copolymerization of a hydrophobic norbornenyl monomer with a hydrophilic monomer containing NHS ester using ring opening metathesis polymerization (ROMP). Subsequent conjugation with peptides was achieved using the NHS moiety. This technique was employed to synthesize enzyme-responsive PPA micelle nanoparticles attached to fluorescent probes for imaging different stages in *in vivo* models of cancer, myocardial infarction, and peripheral artery disease [241–243].

While the graft-to approach generates PPAs with versatile characteristics, the authors utilized a graft-through approach to control spacing and density of bioactive peptides. To achieve this, ROMP was used to generate peptide-polymers with low *Đ*. While ROMP remains a viable strategy for synthesizing graft-through polymerization of peptides with different functionalities, it must be noted that some amino acids in peptide sequences can interact with or coordinate to the metal-based initiators. Therefore, they must be either protected using different functional groups or changes can be made to the peptide sequences while retaining the desired function. Utilizing the graft-through approach, Gianneschi and others demonstrated that PPAs can be particularly used as drug carriers for delivering drugs to diseased tissues with a high loading capacity. Two major issues that need to be addressed when encapsulating drugs inside nanoparticles is (1) to prevent the leakage and burst release of the drug before reaching the targeted tissue, and (2) to pack a significant amount of drug inside the nanoparticle. To address these challenges, PPAs were generated via graft-through polymerization of matrix metalloproteinases (MMP)-responsive peptides together with directly polymerized hydrophobic paclitaxel (PTX) moieties. These drug-loaded polymeric scaffolds assembled into spherical nanoparticles with MMP-responsive peptides forming the outer nano-shell. As these nanoparticles entered the diseased tissue, upregulated MMPs cleaved the peptides thereby releasing the drug into the surrounding tissue. This “trojan horse approach” allowed Gianneschi and co-workers to deliver an exceptionally high dosage of drug by intravenous injection [244].

Expanding on this work, Gianneschi and others have also demonstrated the design of bioactive peptide brush polymers via photoinduced reversible deactivation radical polymerization (photo-RDRP) that is compatible for HTS and HTE [145]. Two bioactive peptide vinyl monomers featuring enzyme-responsive and pro-apoptotic sequences were copolymerized with DMA. This robust synthesis technique that allows preparing bioactive polypeptide brushes using visible light in aqueous solutions, is suitable for HTS approaches and can be easily extended to other small functional peptides that can tolerate these conditions for biological screening. In the case of designing bioactive polymers incorporating bulkier biomolecules, a graft-to approach provides greater versatility for diverse polymer libraries.

Here, we presented applications related to combinatorial polymer chemistry in development of protein-based vaccines, glycopolymers, and polymer-peptide conjugates. Even though many of the required high throughput polymer synthesis and bioconjugation tools exist, HTE and HTS have not been widely employed in these areas of study. This is likely due to the complexity of bioactive polymers compared to other polymer systems discussed. It is evident that incorporating automation and data-driven design into the experimental

workflow of bioactive polymers would result in time and labor reduction while pushing forward innovative developments.

4.5. Automation and Data-Driven Design

Automation tools and data-driven design algorithms have slowly begun making their way into applications related to polymer science. However, data-driven design and the combination of automation and data-driven design have not been featured heavily in drug delivery and biomaterials research. Conversely, the combination of these principles is becoming increasingly prevalent in drug discovery and in the synthesis of small molecule drugs. In this section, we will present state-of-the-art research related to the automation and data-driven design of polymers and small molecule drugs.

4.5.1. Data-Driven Design of Polymers—While high throughput systems aided by breakthrough automated technologies enable researchers to screen polymer therapeutics, HTS can potentially unravel into an inefficient "fishing expedition." Collecting large quantities of data without feedback for improvement is not only inefficient but also adds difficulty in data analysis and interpretation [34–37]. As a result, high throughput work tends to eliminate rational design of the sample set. Paired with HTS, data-driven design and predictive modeling equips scientists with information needed to efficiently select experimental samples or make decisions about whether or not specific polymers are worth exploring [245]. With the emergence of automation in polymer therapeutics, it is important to review published work related to the data-driven design of polymers and assess current capabilities related to polymer therapeutics.

An early example of data-driven design in polymer therapeutics was published by Welsh and co-workers. Their objective was to build a QSPR model to predict cell attachment, cell growth, and fibrinogen absorption of fibroblasts on polymeric surfaces. They created a virtual combinatorial library of 40,000 homopolymers and random heteropolymers using 33 methacrylate monomers with Molecular Operating Environment (MOE) modeling software. A polynomial neural network (PNN) model was built by taking advantage of a training set containing 79 polymers synthesized by a Chemspeed Accelerator SLT100 automated synthesizer [246, 247]. With the input of molecular descriptors from MOE and Dragon software [248, 249], predictions were generated for 13 data points outside of the training set for target property outputs related to polymer biological performance. For each of the three target properties there was a high association between experimental and predictive values ($R^2 > 0.80$) [247].

More recently, there have been a few examples of ML algorithms being developed in polymer science. Wu et al. conducted an ML-based discovery of polymers with high thermal conductivity. Because of limited data on thermal conductivity, Bayesian molecular design was utilized to predict monomer structures related to high T_g and T_m, secondary properties typically related to thermal conductivity. Data used to train this model was obtained from a polymer database PoLyInfo and monomer database QM9. Transfer learning was completed using this data set of secondary properties along with a small data set of thermal conductivity values for fine tuning and ultimately generating thermal conductivity

predictions (Fig. 13). Three monomers were chosen and polymerized for model validation [250].

A few studies have also been completed to mine polymer databases to validate ML algorithms. First, Ramprasad and others designed a protocol to design polymer dielectrics with properties such as electrical insulation and capacitive energy storage. A chemical space was defined based on common chemical groups located on polymers (e.g. CH_2, NH, CO, etc.) and crystal structures were obtained in the Vienna ab initio software package (VASP) from which dielectric constant values could be calculated and databased. Polymer structures were also fingerprinted so they could be databased effectively. This was completed for over 200 polymers from which 90% of the data was used to train a kernel ridge regression (KRR) ML algorithm [165, 251, 252] to predict dielectric property values. There was reasonable agreement between predictions and calculations. Additionally, they used a genetic algorithm to design polymers with target properties, feeding into the predictive KRR algorithm for each design iteration [165]. Kim et al. compared different active learning methods (exploration, exploitation, balanced, and random selection) with a goal of identifying high T_g polymers. However, here they considered a tiny training set (5/736 samples), as all data was obtained from the Polymer Properties Database. In terms of efficiency, or the number of experiments required to obtain 10 polymers with a high T_g, the balanced approach performed the best. Exploitation performed reasonably but contained a high amount of error likely due to overfitting. Additionally, exploitation exhibits the most improvement with larger data sets and with a lower T_g threshold [166]. This study illustrates that it is crucial for scientists to understand the size and quality of the data set, feasibility of the property of interest, and diversity of the chemical space before selecting an ML strategy.

In addition to data-driven design, molecular simulations can elucidate polymer structural properties. In one study, kinetic MC simulations were used to predict the chemical composition of olefin block copolymers synthesized using the chain-shuttling coordination method [253]. One ML algorithm was used to predict structural properties of polymer given a set of experimental inputs (seven different reactant concentrations), while a second algorithm was subsequently developed to predict which experimental inputs would give desired polymer properties. In another study, coarse-grained models of the thermoresponsive polymer poly(N-isoproprylacrylamide) (PNIPAM) were simulated and ML algorithms were used to analyze and evaluate the coil-to-globule phase transition pathways which dictate thermoresponsive behavior [254]. A similar study was also conducted using generic polymer models with MC simulations [255]. ML techniques have also been heavily used as a means of developing and improving new coarse-grained models of polymers [254, 256, 257].

Integrating coarse-grained modeling with ML in data-driven design has also proven promising in a several recent applications. Work by Shmilovich et al. utilized coarse-grained MARTINI simulations of π-conjugated oligopeptides along with active learning and BO to identify molecules that would self-assemble into nanoaggregates [168]. In their approach, iterative CG simulations are performed for candidate molecules whose self-assembly behavior is quantified, the chemical space of the candidates is projected into a low-dimensional latent space, a GP regression model is constructed to connect the latent space to self-assembly behavior, and active learning is combined with the GP model uncertainties to

select new candidates for simulation. Wang et al. employed a very similar approach (combining CG MD simulations with supervised ML and BO) to reveal the QSPR between ionic conductivity and a set of CG model descriptors for solid polymer electrolytes [169]. These recent works demonstrate that simulation, ML, and optimization can be tightly coupled for design of relatively complex soft materials systems. Application of these techniques along with possible integration of automated experimentation and feedback would provide a new frontier for exploration and design of polymer therapeutics and biomaterials.

In summary, applications related to automation, data-driven design, and molecular modeling have slowly appeared in polymer chemistry, however, rarely have they been merged. Initial work has been completed to better design for polymer material and structural properties such as T_g, thermal conductivity, and phase transition pathways. In addition, the application of CG modeling has expanded the utility of computational data for designing soft matter systems. As these algorithms and models increase in complexity, it is expected that this approach would become more applicable to drug delivery and therapeutics-based research.

4.5.2. Automation and Data-Driven Design in Drug Discovery—Currently, data-driven design is more heavily developed and implemented in the areas of drug discovery, organic synthesis, medicinal chemistry, and process chemistry [34, 97, 147] compared to biomaterials and drug delivery. Now that current practices utilizing automation, ML, and data-driven design have been reviewed in polymer science, it is important to examine the same in the space of small molecule pharmaceuticals. As a result, important lessons can be drawn that apply to polymer therapeutics for future expansion.

Automating various chemistries can be a major challenge but can be valuable in reducing the number of repetitive steps that were previously completed manually and minimizing experimental variability. Steiner et al. set out to create a standard programmable and automation-friendly workflow for synthesis of small molecule pharmaceuticals. The user can define the synthesis route with a formal chemical descriptive language (XDL). XDL can be readily converted to chemical assembly (ChASM) language. The user can also input information about physical instrumentation into a GraphML file. The Chempiler system translates ChASM and GraphML code into instructions for the robotic system such as module transfers, priming the system, reagent additions, mixing, changing temperature, extraction, filtration, evaporation, and crystallization. The system also can simulate the code and ensure there are no syntax errors. This group validated programmable robotics by synthesizing small molecules sildenafil, rufinamide, and nytol [258]. The benefit of separating out synthesis scheme and physical hardware information is that the same synthesis procedure can be adopted to other platforms, encouraging collaboration. Additionally, writing ChASM and GraphML code is relatively straightforward, making this workflow accessible to those who have limited programming experience.

These automation technologies for chemical synthesis can be enhanced when the loop is closed between synthesis and characterization. Christensen et al. demonstrated this by developing a setup to implement automated kinetic profiling of a Suzuki cross-coupling reaction by HPLC with UV detection. A Chemspeed Swing liquid handling robot sampled

the reaction volume and interfaced with an Agilent 1100 Series HPLC. A two-position valve and fluidic linkage enabled one-way communication from the robot to HPLC via an electrical stimulus that activated the HPLC run. The Chemspeed Autosuite software contained valve and HPLC control. Through automated kinetic profiling, reaction conditions were identified to yield a five-fold reaction rate increase [133].

Another major obstacle in organic synthesis of small molecule therapeutics is planning synthesis steps. This requires extensive expertise but even so may entail painstaking effort to optimize. Coley et al. leveraged ML and AI to aid in organic synthesis planning and to complete reactions in a rapid, automated manner. They linked computer-aided synthesis planning (CASP), synthetic route creation, and robotic synthesis (Fig. 14). From the Reaxys database, about 15 million reaction outcomes were input into the ANN model for CASP. For data augmentation, over 100 million cases of minor additional products for the given reactions were fed into the algorithm to serve as negative reaction outcomes [259, 260]. The user can input the molecule of interest into the software which accepts SMILES format of molecular identification. Chemical recipe files (CRFs) are output to contain reaction conditions and only require the user to provide stoichiometries. Once finalized, the robotic platform executes the reaction. This platform consists of a UR3 six-axis manipulator that can arrange modules (reactors and separators) from a storage area while there is automated control of pumps, fluidic delivery, waste removal, and extraction [259].

As shown in this section, data-driven design and molecular modeling are becoming more widely utilized for polymer design of material properties and structural parameters. Moving forward, it will be critical to combine many of the techniques described in this review in the drug delivery space in a design-build-test-learn workflow to improve experimental design and efficiency. An outlook for doing so is provided in Section 5.

5. Perspective on Polymer Therapeutics and Bioactive Polymers

With the promise of automation and data-driven design in applications highlighted in Section 4, we will now focus on understanding how these concepts can be advanced in drug delivery and biomaterials research. As shown in Section 4.5.2, automation and data-driven design are more fully integrated in drug discovery research. Here, we will draw lessons from the advances in drug discovery research for polymer therapeutics, underscore some limitations, and discuss trends relevant to work in polymer chemistry, drug delivery, and biomaterials.

5.1. Lessons for Polymer Therapeutics and Bioactive Polymers

In polymer therapeutics and biomaterials, the sequence of design-build-test-learn is typically done [32]. Once testing is completed, experimenters can glean useful information that can be utilized for the next phase of experimentation. However, in the realm of HTE and HTS with massive data sets, the gap between testing and redesign can be immense given the difficulty in not only analyzing but also learning from such data. By incorporating ML and AI into high throughput experiments, the time lag between testing and redesign can be significantly reduced. This process can only be enhanced by a standardized and automated method of databasing an enormous amount of data. Not only does this ease internal data handling, but

it also fosters collaborations and ensures rigor and reproducibility. As described previously, there is a methodology and database to concisely list important structural parameters for small molecule compounds [259–262]. Progress towards a cheminformatics approach in polymer science has been made through the creation of an indexing system, but there are some additional experimental details that could be databased [147, 153].

In the automation realm, there are various design considerations. In general, a modular, customizable approach is preferable because it offers the flexibility to carry out multiple types of experiments while testing experimental conditions in a parallel format. It also allows for interaction with ML and AI algorithms that generate input files and code [10, 97, 112, 113, 258]. Robotic arms and grippers give robotic systems greater versatility with the ability to integrate with characterization by GPC, HPLC, DLS, or UV-Vis plate readers for both optimizing conditions and full-scale testing [95, 133, 135, 263, 264].

As polymer therapeutics and materials science improve throughput, perhaps the most important rule will be to avoid large-scale “fishing expeditions.” It is crucial to understand how much data can be generated by the synthetic process and to never operate at excess capacity. Researchers should not squander time generating a large quantity of data without sufficient feedback [34–39]. Additionally, designing an appropriate data-driven design algorithm is vital because it will ensure quality post-experimentation feedback [147, 166, 251, 252].

5.2. Limitations

Despite its promise, an automation and data-driven design approach comes with its drawbacks. For one, automation instrumentation can be cost prohibitive and can require resources and expertise to set up and use, making accessibility improvements for the end user critical. False positives and negatives can also occur, so it is necessary to include sufficient controls within each experiment or set of parallelized reactions (e.g. in each 96-well plate) and track if these controls shift over time [26]. Especially in polymer science, there can be difficulty automating the handling of solids, so powder dispensing would likely only be useful in preparing reagents or stock solutions [95]. Viscosity can also be a concern for liquid handling so monitoring solutions and minimizing concentrations would be required [110]. Other challenges include implementation of a controlled, versatile polymerization mechanism and ambiguity associated with “scoring” criteria that determine success and failure [34, 135, 261].

Other challenges are related to the big data component of HTE and HTS. To reduce the likelihood of embarking on a “fishing expedition,” proper design is needed to not strain the high throughput workflow or test too many parameters. This type of screening of over 100,000 compounds in one phase of experimentation is overly inefficient because data analysis becomes impractical without ML/AI tools. This is especially true with data sets that are non-linear or not intuitive, due to the nature of the structure-activity relationship, randomness, experimental or analytical error, or data fragmentation [26, 34]. ML and AI require a large data set for experimental validation, but this does not currently exist in polymer therapeutics in the form of data repositories. While some resources exist such as TensorFlow and scikit-learn, the polymer science community lacks a centralized location to

house data. Additionally, polymer nomenclature and storing relevant information can be complex. There is not a consensus on polymer naming conventions in the polymer science community, but it is also problematic to store information pertaining to structure, architecture, branching, composition, chirality, synthetic route, and experimental conditions. Polymer informatics is crucial for the design-build-test-learn workflow [26, 34, 147, 148].

However, as new molecular entities (NMEs), novel polymers can be challenging to approve and arrive to market. This is due to extensive regulatory requirements, high research and development costs from the benchtop to clinical trials, and the difficulty of identifying optimal polymers [265–267]. To a certain extent, the high throughput, automated, and ML/AI approach described in this review should alleviate these concerns. Researchers should also be mindful that variations in physicochemical parameters can have a major effect on performance. For instance, it was found that molecular weight and $Đ$ of polymers used in ASDs, along with processing conditions, has a significant effect on drug supersaturation and precipitation inhibition [268]. With important parameters in mind, insightful characterization methods can be built into high throughput workflows.

On the execution side, a balance is essential between automation and ML/AI. This balance is impossible to design especially with variations in group-to-group throughput capabilities. By attaining an optimal number of design-synthesize-test loops, the feedback obtained and thus efficiency can be maximized [34]. Misconceptions exist about ML and AI, so it is the responsibility of researchers to accurately describe the capabilities and potential of these techniques when communicating findings. As is the case with any cutting-edge technology, it will be challenging to shift community perceptions [261].

5.3. Trends and Future Direction

It is important to be aware of some trends that exist to understand the future direction of polymer therapeutics and bioactive polymers. As previously described, storing structural and experimental information is a difficult task because polymer nomenclature is not clearly defined to include important traits such as composition, architecture, chirality, and more in a concise manner. For instance, a structural representation system based on SMILES, BigSMILES, was developed in 2019 to include stochastic polymers [153, 269, 270]. The authors state that this language is succinct, accessible, and can accommodate many applications. They demonstrated its ability to describe and notate bonds, fragment names, stochastic objects, branched polymers, end groups, macrocycles, ladder polymers, and polymers with repeating units. BigSMILES could be a practical language for describing and databasing polymer information as it can also be utilized for molecular fingerprinting, a practice that is useful in ML involving small molecule drugs. If a transition takes place towards a design-build-test-learn scheme, large scale data management will become crucial [26, 32, 135]. With the ability to organize extensive databases, it will be possible to employ an ML or AI algorithm beforehand to aid in initial experimental design as well as reduce costs and labor [165, 166].

As previously described in Table 1, many liquid handling robotics can interface with external instrumentation, often useful for synthesis or characterization. As these instruments continue to develop, there will likely be an advancement of complementary robotic

components (e.g. robotic arms and grippers) to achieve greater degrees of freedom of physical manipulation with a high level of autonomy [271]. Another exciting possibility is the development of characterization instrumentation that will be crucial for the “test” component of a design-build-test-learn workflow. As shown in Figure 5, chromatography experienced a major shift towards becoming high throughput friendly over the past 20-30 years. It is reasonable to expect this trend to continue in characterization, as it is becoming more realistic to conduct experiments without human intervention. A shift in polymer science towards high throughput, as described in numerous publications by our group and others [9–12, 14, 19, 20, 31, 32, 76, 135], will allow researchers to take this approach in biomaterials and drug delivery.

6. Conclusion

Polymers are incredible materials that can be tuned in various ways depending on the application. With current synthesis capability, scientists can vary molecular weight, architecture, composition, stereochemistry, valency, and other parameters. We reviewed several combinatorial and high throughput approaches that took advantage of this large chemical space in antimicrobials, gene delivery, and drug delivery. Each of these research areas has expanded into the realm of robotics and automation in different ways to aid in polymer synthesis or complete several pipetting steps that would otherwise be done manually. Because of the emergence of AI and ML in the pharmaceutical industry to complement automation in the development of small molecule therapeutics, we found it crucial to review some of this work and begin uncovering insights that could be utilized and accessible to the drug delivery and biomaterials space. This is an exciting time period as we are rapidly approaching an inflection point in this community where data-driven design can ultimately boost research productivity and accelerate progress.

Acknowledgements

RU and MT were supported by the National Institutes of General Medical Sciences of the National Institutes of Health under Award T32 GM008339. RU was also supported by the New Jersey Commission on Cancer Research (NJCCR) Pre-Doctoral Research Fellowship under the New Jersey Department of Health. TM was supported by NIH award K12GM093854.

References

[1]. Rudra A, Li J, Shakur R, Bhagchandani S, Langer R, Trends in Therapeutic Conjugates: Bench to Clinic, Bioconjug. Chem, 31 (2020) 462–473. [PubMed: 31990184]

[2]. Chu TW, Kopeček J, Drug-free macromolecular therapeutics-a new paradigm in polymeric nanomedicines, Biomater. Sci, 3 (2015) 908–922. [PubMed: 26191406]

[3]. Du AW, Stenzel MH, Drug Carriers for the Delivery of Therapeutic Peptides, Biomacromolecules, 15 (2014) 1097–1114. [PubMed: 24661025]

[4]. Russo D, de Angelis A, Garvey CJ, Wurm FR, Appavou MS, Prevost S, Effect of Polymer Chain Density on Protein-Polymer Conjugate Conformation, Biomacromolecules, 20 (2019) 1944–1955. [PubMed: 30933481]

[5]. Ekladious I, Colson YL, Grinstaff MW, Polymer-drug conjugate therapeutics: advances, insights and prospects, Nat. Rev. Drug Discov, 18 (2019) 273–294. [PubMed: 30542076]

[6]. Ko JH, Maynard HD, A guide to maximizing the therapeutic potential of protein-polymer conjugates by rational design, Chem. Soc. Rev, 47 (2018) 8998–9014. [PubMed: 30443654]

[7]. Acar H, Ting JM, Srivastava S, LaBelle JL, Tirrell MV, Molecular engineering solutions for therapeutic peptide delivery, Chem. Soc. Rev, 46 (2017) 6553–6569. [PubMed: 28902203]

[8]. Ting JM, Porter WW III, Mecca JM, Bates FS, Reineke TM, Advances in Polymer Design for Enhancing Oral Drug Solubility and Delivery, Bioconjug. Chem, 29 (2018) 939–952. [PubMed: 29319295]

[9]. Gormley AJ, Yeow J, Ng G, Conway O, Boyer C, Chapman R, An Oxygen-Tolerant PET-RAFT Polymerization for Screening Structure-Activity Relationships, Angew. Chem. Int. Ed, 57 (2018) 1557–1562.

[10]. Tamasi M, Kosuri S, DiStefano J, Chapman R, Gormley AJ, Automation of Controlled/Living Radical Polymerization, Advanced Intelligent Systems, 2 (2020) 1–8.

[11]. Chapman R, Gormley AJ, Herpoldt K, Stevens MM, Highly controlled open vessel RAFT polymerizations by enzyme degassing, Macromolecules, 47 (2014) 8541–8547.

[12]. Chapman R, Gormley AJ, Stenzel MH, Stevens MM, Combinatorial low-volume synthesis of well-defined polymers by enzyme degassing, Angew. Chem. Int. Ed, 128 (2016) 4576–4579.

[13]. Xu J, Jung K, Atme A, Shanmugam S, Boyer C, A Robust and Versatile Photoinduced Living Polymerization of Conjugated and Unconjugated Monomers and Its Oxygen Tolerance, J. Am. Chem. Soc, 136 (2014) 5508–5519. [PubMed: 24689993]

[14]. Enciso AE, Fu L, Russell AJ, Matyjaszewski K, A Breathing Atom-Transfer Radical Polymerization: Fully Oxygen-Tolerant Polymerization Inspired by Aerobic Respiration of Cells, Angew. Chem. Int. Ed, 130 (2018) 945–948.

[15]. Ting JM, Tale S, Purchel AA, Jones SD, Widanapathirana L, Tolstyka ZP, Guo L, Guillaudeu SJ, Bates FS, Reineke TM, High-Throughput Excipient Discovery Enables Oral Delivery of Poorly Soluble Pharmaceuticals, ACS Cent. Sci, 2 (2016) 748–755. [PubMed: 27800558]

[16]. Ting JM, Navale TS, Bates FS, Reineke TM, Precise Compositional Control and Systematic Preparation of Multimonomeric Statistical Copolymers, ACS Macro Lett, 2 (2013) 770–774.

[17]. Shanmugam S, Boyer C, Stereo-, Temporal and Chemical Control through Photoactivation of Living Radical Polymerization: Synthesis of Block and Gradient Copolymers, J. Am. Chem. Soc, 137 (2015) 9988–9999. [PubMed: 26171943]

[18]. Isobe Y, Fujioka D, Habaue S, Okamoto Y, Efficient Lewis acid-catalyzed stereocontrolled radical polymerization of acrylamides, J. Am. Chem. Soc, 123 (2001) 7180–7181. [PubMed: 11459507]

[19]. Upadhya R, Murthy NS, Hoop CL, Kosuri S, Nanda V, Kohn J, Baum J, Gormley AJ, PET-RAFT and SAXS: High Throughput Tools To Study Compactness and Flexibility of Single-Chain Polymer Nanoparticles, Macromolecules, 52 (2019) 8295–8304. [PubMed: 33814613]

[20]. Li Z, Kosuri S, Foster H, Cohen J, Jumeaux C, Stevens MM, Chapman R, Gormley AJ, A Dual Wavelength Polymerization and Bioconjugation Strategy for High Throughput Synthesis of Multivalent Ligands, J. Am. Chem. Soc, 141 (2019) 19823–19830. [PubMed: 31743014]

[21]. Lueckerath T, Strauch T, Koynov K, Barner-Kowollik C, Ng DY, Weil T, DNA-Polymer Conjugates by Photoinduced RAFT Polymerization, Biomacromolecules, 20 (2019) 212–221. [PubMed: 30407801]

[22]. Lynn GM, Laga R, Darrah PA, Ishizuka AS, Balaci AJ, Dulcey AE, Pechar M, Pola R, Gerner MY, Yamamoto A, Buechler CR, Quinn KM, Smelkinson MG, Vanek O, Cawood R, Hills T, Vasalatiy O, Kastenmuller K, Francica JR, Stutts L, Tom JK, Ryu KA, Esser-Kahn AP, Etrych T, Fisher KD, Seymour LW, Seder RA, In vivo characterization of the physicochemical properties of polymer-linked TLR agonists that enhance vaccine immunogenicity, Nat. Biotechnol, 33 (2015) 1201–1210. [PubMed: 26501954]

[23]. Theodorou A, Liarou E, Haddleton DM, Stavrakaki IG, Skordalidis P, Whitfield R, Anastasaki A, Velonia K, Protein-polymer bioconjugates via a versatile oxygen tolerant photoinduced controlled radical polymerization approach, Nat Commun, 11 (2020) 1–11. [PubMed: 31911652]

[24]. Richards SJ, Jones A, Tomás RMF, Gibson MI, Photochemical “In-Air” Combinatorial Discovery of Antimicrobial Co-polymers, Chem. Eur. J, 24 (2018) 13758–13761. [PubMed: 30069965]

[25]. Jiang X, Halmes AJ, Licari G, Smith JW, Song Y, Moore EG, Chen Q, Tajkhorshid E, Rienstra CM, Moore JS, Multivalent Polymer-Peptide Conjugates: A General Platform for Inhibiting Amyloid Beta Peptide Aggregation, ACS Macro Lett, 8 (2019) 1365–1371. [PubMed: 32149017]

[26]. Maier WF, Early Years of High-Throughput Experimentation and Combinatorial Approaches in Catalysis and Materials Science, ACS Comb Sci, 21 (2019) 437–444. [PubMed: 30939240]

[27]. Thompson LA, Ellman JA, Synthesis and applications of small molecule libraries, Chem. Rev, 96 (1996) 555–600. [PubMed: 11848765]

[28]. Gordon EM, Gallop MA, Patel DV, Strategy and tactics in combinatorial organic synthesis. Applications to drug discovery, Ace. Chem. Res, 29 (1996) 144–154.

[29]. Balkenhohl F, von dem Bussche-Hünnefeld C, Lansky A, Zechel C, Combinatorial synthesis of small organic molecules, Angew. Chem. Int. Ed, 35 (1996) 2288–2337.

[30]. Mishra B, Wilson DR, Sripathi SR, Suprenant MP, Rui Y, Wahlin KJ, Berlinicke C, Green JJ, Zack DJ, Combinatorial library of biodegradable polyesters enables delivery of plasmid DNA to polarized human RPE monolayers for retinal gene therapy, Regen. Eng. Transl. Med, (2019) 1–13. [PubMed: 30976657]

[31]. Yeow J, Chapman R, Gormley AJ, Boyer C, Up in the air: oxygen tolerance in controlled/living radical polymerisation, Chem. Soc. Rev, 47 (2018) 4357–4387. [PubMed: 29718038]

[32]. Oliver S, Zhao L, Gormley AJ, Chapman R, Boyer C, Living in the Fast Lane - High Throughput Controlled/Living Radical Polymerization, Macromolecules, 52 (2018) 3–23.

[33]. Yeow J, Chapman R, Xu J, Boyer C, Oxygen tolerant photopolymerization for ultralow volumes, Polym. Chem, 8 (2017) 5012–5022.

[34]. Schneider G, Automating drug discovery, Nat. Rev. Drug Discov, 17 (2018) 97–113. [PubMed: 29242609]

[35]. Barker J, Hesterkamp T, Whittaker M, Integrating HTS and fragment-based drug discovery, Drug Discovery World, 9 (2008) 69–75.

[36]. Kubinyi H, Drug research: myths, hype and reality, Nat. Rev. Drug Discov, 2 (2003) 665–668. [PubMed: 12904816]

[37]. Ajay WP Waters MA. Murcko, Can We Learn To Distinguish between “Drug-like” and “Nondrug-like” Molecules?, J. Med. Chem, 41 (1998) 3314–3324. [PubMed: 9719583]

[38]. Sadowski J, Kubinyi H, A scoring scheme for discriminating between drugs and nondrugs, J. Med. Chem, 41 (1998) 3325–3329. [PubMed: 9719584]

[39]. Potyrailo R, Rajan K, Stoewe K, Takeuchi I, Chisholm B, Lam H, Combinatorial and High-Throughput Screening of Materials Libraries: Review of State of the Art, ACS Comb Sci, 13 (2011) 579–633. [PubMed: 21644562]

[40]. Tian S, Wang J, Li Y, Li D, Xu L, Hou T, The application of in silico drug-likeness predictions in pharmaceutical research, Adv. Drug Deliv. Rev, 86 (2015) 2–10. [PubMed: 25666163]

[41]. Henstock PV, Artificial Intelligence for Pharma: Time for Internal Investment, Trends Pharmacol. Sci, 40 (2019) 543–546. [PubMed: 31204059]

[42]. Struble TJ, Alvarez JC, Brown S, Chytil M, Cisar J, DesJarlais R, Engkvist O, Frank SA, Greve DR, Griffin DJ, Hou X, Johannes JW, Kreatsoulas C, Lahue B, Mathea M, Mogk G, Nicolaou CA, Palmer AD, Price DJ, Robinson RI, Salentin S, Xing L, Jaakkola T, Green WH, Barzilay R, Coley CW, Jensen KF, Current and Future Roles of Artificial Intelligence in Medicinal Chemistry Synthesis, J. Med. Chem, 63 (2020) 8667–8682. [PubMed: 32243158]

[43]. Brocchini S, James K, Tangpasuthadol V, Kohn J, A combinatorial approach for polymer design, J. Am. Chem. Soc, 119 (1997) 4553–4554.

[44]. Brocchini KJS, Tangpasuthadol V, Kohn J, Structure–property correlations in a combinatorial library of degradable biomaterials, J. Biomed. Mater. Res, 42 (1998) 66–75. [PubMed: 9740008]

[45]. Bosman AW, Heumann A, Klaemer G, Benoit D, Fréchet JM, Hawker CJ, High-Throughput Synthesis of Nanoscale Materials: Structural Optimization of Functionalized One-Step Star Polymers, J. Am. Chem. Soc, 123 (2001) 6461–6462. [PubMed: 11427091]

[46]. Becer CR, Hahn S, Fijten MW, Thijs HM, Hoogenboom R, Schubert US, Libraries of Methacrylic Acid and Oligo(ethylene glycol) Methacrylate Copolymers with LCST Behavior, J. Polym. Sci. A Polym. Chem, 46 (2008)7138–7147.

[47]. Yang J, Mei Y, Hook AL, Taylor M, Urquhart AJ, Bogatyrev SR, Langer R, Anderson DG, Davies MC, Alexander MR, Polymer surface functionalities that control human embryoid body cell adhesion revealed by high throughput surface characterization of combinatorial material microarrays, Biomaterials, 31 (2010) 8827–8838. [PubMed: 20832108]

[48]. Yang F, Cho SW, Son SM, Hudson SP, Bogatyrev S, Keung L, Kohane DS, Langer R, Anderson DG, Combinatorial Extracellular Matrices for Human Embryonic Stem Cell Differentiation in 3D, Biomacromolecules, 11 (2010) 1909–1914. [PubMed: 20614932]

[49]. Patel AK, Celiz AD, Rajamohan D, Anderson DG, Langer R, Davies MC, Alexander MR, Denning C, A defined synthetic substrate for serum-free culture of human stem cell derived cardiomyocytes with improved functional maturity identified using combinatorial materials microarrays, Biomaterials, 61 (2015) 257–265. [PubMed: 26005764]

[50]. Yang F, Mei Y, Langer R, Anderson DG, High Throughput Optimization of Stem Cell Microenvironments, Comb. Chem. High Throughput Screen, 12 (2009) 554–561. [PubMed: 19601753]

[51]. Epa VC, Yang J, Mei Y, Hook AL, Langer R, Anderson DG, Davies MC, Alexander MR, Winkler DA, Modelling human embryoid body cell adhesion to a combinatorial library of polymer surfaces, J. Mater. Chem, 22 (2012) 20902–20906. [PubMed: 24092955]

[52]. Mei Y, Saha K, Bogatyrev SR, Yang J, Hook AL, Kalcioglu ZI, Cho SW, Mitalipova M, Pyzocha N, Rojas F, Van Vliet KJ, Davies MC, Alexander MR, Langer R, Jaenisch R, Anderson DG, Combinatorial development of biomaterials for clonal growth of human pluripotent stem cells, Nat. Mater, 9 (2010) 768–778. [PubMed: 20729850]

[53]. Anderson DG, Tweedie CA, Hossain N, Navarro SM, Brey DM, Van Vliet KJ, Langer R, Burdick JA, A combinatorial library of photocrosslinkable and degradable materials, Adv. Mater, 18 (2006) 2614–2618.

[54]. Tweedie CA, Anderson DG, Langer R, Van Vliet KJ, Combinatorial material mechanics: High-throughput polymer synthesis and nanomechanical screening, Adv. Mater, 17 (2005) 2599–2604.

[55]. Urquhart AJ, Anderson DG, Taylor M, Alexander MR, Langer R, Davies MC, High throughput surface characterisation of a combinatorial material library, Adv. Mater, 19 (2007) 2486–2491.

[56]. Davies MC, Alexander MR, Hook AL, Yang J, Mei Y, Taylor M, Urquhart AJ, Langer R, Anderson DG, High throughput surface characterization: A review of a new tool for screening prospective biomedical material arrays, J. Drug Target., 18 (2010) 741–751. [PubMed: 20945971]

[57]. Goldberg M, Mahon K, Anderson D, Combinatorial and rational approaches to polymer synthesis for medicine, Adv. Drug Deliv. Rev, 60 (2008) 971–978. [PubMed: 18423930]

[58]. Becker G, Wurm FR, Functional biodegradable polymers via ring-opening polymerization of monomers without protective groups, Chem. Soc. Rev, 47 (2018) 7739–7782. [PubMed: 30221267]

[59]. Zhang XC, Macdonald DA, Goosen MFA, Mcauley KB, Mechanism of Lactide Polymerization in the Presence of Stannous Octoate - the Effect of Hydroxy and Carboxylic-Acid Substances, J. Polym. Sci. A Polym. Chem, 32 (1994) 2965–2970.

[60]. Gleede T, Rieger E, Liu L, Bakkali-Hassani C, Wagner M, Carlotti S, Taton D, Andrienko D, Wurm FR, Alcohol- and Water-Tolerant Living Anionic Polymerization of Aziridines, Macromolecules, 51 (2018) 5713–5719.

[61]. Nagai A, Ochiai B, Endo T, Living cationic ring-opening polymerization by water-stable initiator: synthesis of a well-defined optically active polythiourethane, ChemComm, 24 (2003) 3018–3019.

[62]. Wu Y, Zhang D, Ma P, Zhou R, Hua L, Liu R, Lithium hexamethyldisilazide initiated superfast ring opening polymerization of alpha-amino acid N-carboxyanhydrides, Nat. Commun, 9 (2018) 1–10. [PubMed: 29317637]

[63]. Rolland M, Whitfield R, Messmer D, Parkatzidis K, Truong NP, Anastasaki A, Effect of Polymerization Components on Oxygen-Tolerant Photo-ATRP, ACS Macro Lett, 8 (2019) 1546–1551.

[64]. Ng G, Yeow J, Xu J, Boyer C, Application of oxygen tolerant PET-RAFT to polymerization-induced self-assembly, Polym. Chem, 8 (2017) 2841–2851.

[65]. Yeow J, Shanmugam S, Corrigan N, Kuchel RP, Xu J, Boyer C, A Polymerization-Induced Self-Assembly Approach to Nanoparticles Loaded with Singlet Oxygen Generators, Macromolecules, 49 (2016) 7277–7285.

[66]. Corrigan N, Rosli D, Jones JWJ, Xu J, Boyer C, Oxygen Tolerance in Living Radical Polymerization: Investigation of Mechanism and Implementation in Continuous Flow Polymerization, Macromolecules, 49 (2016) 6779–6789.

[67]. Stubbs C, Congdon T, Davis J, Lester D, Richards SJ, Gibson MI, High-Throughput Tertiary Amine Deoxygenated Photopolymerizations for Synthesizing Polymer Libraries, Macromolecules, 52 (2019) 7603–7612. [PubMed: 31656323]

[68]. Gurnani P, Floyd T, Tanaka J, Stubbs C, Lester D, Sanchez-Cano C, Perrier S, PCR-RAFT: rapid high throughput oxygen tolerant RAFT polymer synthesis in a biology laboratory, Polym. Chem, 11 (2020) 1230–1236.

[69]. Hughes I, Hunter D, Techniques for analysis and purification in high-throughput chemistry, Curr. Opin. Chem. Biol, 5 (2001) 243–247. [PubMed: 11479114]

[70]. Fagan JA, Khripin CY, Silvera Batista CA, Simpson JR, Haroz EH, Hight Walker AR, Zheng M, Isolation of Specific Small-Diameter Single-Wall Carbon Nanotube Species via Aqueous Two-Phase Extraction, Adv. Mater, 26 (2014) 2800–2804. [PubMed: 24448916]

[71]. Schmatloch S, Meier MAR, Schubert US, Instrumentation for combinatorial and high-throughput polymer research: A short overview, Macromol. Rapid Comm, 24 (2003) 33–46.

[72]. Chighine A, Sechi G, Bradley M, Tools for efficient high-throughput synthesis, Drug Discov. Today, 12 (2007) 459–464. [PubMed: 17532530]

[73]. Hughes I, Separating the Wheat from the Chaff: High Throughput Purification of Chemical Libraries, SLAS Technol, 5 (2000) 69–71.

[74]. Hoogenboom R, Schubert US, The fast and the curious: High-throughput experimentation in synthetic polymer chemistry, J. Polym. Sci. A Pol. Chem, 41 (2003) 2425–2434.

[75]. Wang SQ, Fu CK, Wei Y, Tao L, Facile One- Pot Synthesis of New Functional Polymers through Multicomponent Systems, Macromol. Chem. Phys, 215 (2014) 486–492.

[76]. Upadhya R, Kanagala MJ, Gormley AJ, Purifying Low-Volume Combinatorial Polymer Libraries with Gel Filtration Columns, Macromol. Rapid Comm, 40 (2019) 1–5.

[77]. Schuett T, Kimmig J, Zechel S, Schubert US, Automated Polymer Purification Using Dialysis, Polymers-Basel, 12 (2020) 2095.

[78]. Lounnas V, Ritschel T, Kelder J, McGuire R, Bywater RP, Foloppe N, Current progress in Structure-Based Rational Drug Design marks a new mindset in drug discovery, Comput. Struct. Biotechnol. J, 5 (2013) e201302011. [PubMed: 24688704]

[79]. Tasdelen MA, Diels–Alder “click” reactions: recent applications in polymer and material science, Polym. Chem, 2 (2011) 2133–2145.

[80]. Machida T, Lang K, Xue L, Chin JW, Winssinger N, Site-Specific Glycoconjugation of Protein via Bioorthogonal Tetrazine Cycloaddition with a Genetically Encoded trans-Cyclooctene or Bicyclononyne, Bioconjugate Chem, 26 (2015) 802–806

[81]. Debets MF, Prins JS, Merkx D, van Berkel SS, van Delft FL, van Hest JC, Rutjes FP, Synthesis of DIBAC analogues with excellent SPAAC rate constants, Org. Biomol. Chem, 12 (2014) 5031–5037. [PubMed: 24899166]

[82]. Hansell CF, Espeel P, Stamenovic MM, Barker IA, Dove AP, Du Prez FE, O’Reilly RK, Additive-free clicking for polymer functionalization and coupling by tetrazine–norbomene chemistry, J. Am. Chem. Soc, 133 (2011) 13828–13831. [PubMed: 21819063]

[83]. Hansell CF, O’Reilly RK, A “mix-and-click” approach to double core–shell micelle functionalization, ACS Macro Lett, 1 (2012) 896–901.

[84]. Lowe AB, Thiol-ene “click” reactions and recent applications in polymer and materials synthesis, Polym. Chem, 1 (2010) 17–36.

[85]. Campos LM, Killops KL, Sakai R, Paulusse JM, Damiron D, Drockenmuller E, Messmore BW, Hawker CJ, Development of thermal and photochemical strategies for thiol– ene click polymer functionalization, Macromolecules, 41 (2008) 7063–7070.

[86]. Blasco E, Sims MB, Goldmann AS, Sumerlin BS, Barner-Kowollik C, 50th anniversary perspective: Polymer functionalization, Macromolecules, 50 (2017) 5215–5252.

[87]. Goldmann AS, Glassner M, Inglis AJ, Barner-Kowollik C, Post-Functionalization of Polymers via Orthogonal Ligation Chemistry, Macromol. Rapid Comm, 34 (2013) 810–849.

[88]. Gauthier MA, Gibson MI, Klok HA, Synthesis of Functional Polymers by Post-Polymerization Modification, Angew. Chem. Int. Ed, 48 (2009) 48–58.

[89]. Poloukhtine AA, Mbua NE, Wolfert MA, Boons GJ, Popik VV, Selective Labeling of Living Cells by a Photo-Triggered Click Reaction, J. Am. Chem. Soc, 131 (2009) 15769–15776. [PubMed: 19860481]

[90]. Qu L, Wu Y, Sun P, Zhang K, Liu ZP, Cyclopropenone-masked dibenzocyclooctyne end-functionalized polymers from reversible addition-fragmentation chain transfer polymerization, Polymer, 114 (2017) 36–43.

[91]. Sun P, Yan G, Tang Q, Chen Y, Zhang K, Well-defined cyclopropenone-masked dibenzocyclooctyne functionalized polymers from atom transfer radical polymerization, Polymer, 64 (2015) 202–209.

[92]. Yang X, Wang S, Yan Y, Wu Y, Zhang K, Chen Y, Well-defined dibenzocyclooctyne end functionalized polymers from atom transfer radical polymerization, Polymer, 55 (2014) 1128–1135.

[93]. Shevlin M, Practical High-Throughput Experimentation for Chemists, ACS Med. Chem. Lett, 8 (2017) 601–607. [PubMed: 28626518]

[94]. Campos KR, Coleman PJ, Alvarez JC, Dreher SD, Garbaccio RM, Terrett NK, Tillyer RD, Truppo MD, Parmee ER, The importance of synthetic chemistry in the pharmaceutical industry, Science, 363 (2019) 1–8.

[95]. Bahr MN, Damon DB, Yates SD, Chin AS, Christopher JD, Cromer S, Perrotto N, Quiroz J, Rosso V, Collaborative Evaluation of Commercially Available Automated Powder Dispensing Platforms for High-Throughput Experimentation in Pharmaceutical Applications, Org. Process Res. Dev, 22 (2018) 1500–1508.

[96]. Selekman JA, Qiu J, Tran K, Stevens J, Rosso V, Simmons E, Xiao Y, Janey J, High-Throughput Automation in Chemical Process Development, Annu. Rev. Chem. Biomol. Eng, 8 (2017) 525–547. [PubMed: 28460183]

[97]. Mennen SM, Alhambra C, Allen CL, Barberis M, Berritt S, Brandt TA, Campbell AD, Castanon J, Chemey AH, Christensen M, Damon DB, de Diego JE, Garcia-Cerrada S, Garcia-Losada P, Haro R, Janey J, Leitch DC, Li L, Liu FF, Lobben PC, MacMillan DWC, Magano J, McInturff E, Monfette S, Post RJ, Schultz D, Sitter BJ, Stevens JM, Strambeanu JI, Twilton J, Wang K, Zajac MA, The Evolution of High-Throughput Experimentation in Pharmaceutical Development and Perspectives on the Future, Org. Process Res. Dev, 23 (2019) 1213–1242.

[98]. Vasilevich A, de Boer J, Robot-scientists will lead tomorrow's biomaterials discovery, Curr. Opin. Biomed. Eng, 6 (2018) 74–80.

[99]. Nunn C, DiPietro A, Hodnett N, Sun P, Wells KM, High-Throughput Automated Design of Excipients (DoE) and Kinetic Modeling to Aid in Process Development of an API, Org. Process Res. Dev, 22 (2018) 54–61.

[100]. Hoogenboom R, Fijten MWM, Meier MAR, Schubert US, Living cationic polymerizations utilizing an automated synthesizer: High-throughput synthesis of polyoxazolines, Macromol. Rapid Comm, 24 (2003) 92–97.

[101]. Hoogenboom R, Wiesbrock F, Leenen MAM, Meier MAR, Schubert US, Accelerating the living polymerization of 2-nonyl-2-oxazoline by implementing a microwave synthesizer into a high-throughput experimentation worknow, J. Comb. Chem, 7 (2005) 10–13. [PubMed: 15638473]

[102]. Lin BH, Hedrick JL, Park NH, Waymouth RM, Programmable High-Throughput Platform for the Rapid and Scalable Synthesis of Polyester and Polycarbonate Libraries, J. Am. Chem. Soc, 141 (2019) 8921–8927. [PubMed: 31117549]

[103]. Guerrero-Sanchez C, Paulus RM, Fijten MWM, de la Mar MJ, Hoogenboom R, Schubert US, High-throughput experimentation in synthetic polymer chemistry: From RAFT and anionic polymerizations to process development, Appl. Surf. Sci, 252 (2006) 2555–2561.

[104]. Paulus RM, Fijten MWM, de la Mar MI, Hoogenboom R, Schubert US, Reversible addition-fragmentation chain transfer polymerization on different synthesizer platforms, QSAR Comb. Sci, 24 (2005) 863–867.

[105]. Guerrero-Sanchez C, Keddie DJ, Saubem S, Chiefari J, Automated Parallel Freeze-Evacuate-Thaw Degassing Method for Oxygen-Sensitive Reactions: RAFT Polymerization, ACS Comb. Sci, 14 (2012) 389–394. [PubMed: 22709484]

[106]. Rosales-Guzman M, Perez-Camacho O, Guerrero-Sanchez C, Harrisson S, Torres-Lubian R, Vitz J, Schubert US, Saldivar-Guerra E, Semiautomated Parallel RAFT Copolymerization of Isoprene with Glycidyl Methacrylate, ACS Comb. Sci, 21 (2019) 771–781. [PubMed: 31626530]

[107]. Zhang HQ, Hoogenboom R, Meier MAR, Schubert US, Combinatorial and high-throughput approaches in polymer science, Meas. Sci. Technol, 16 (2005) 203–211.

[108]. Hoogenboom R, Meier MAR, Schubert US, Combinatorial methods, automated synthesis and high-throughput screening in polymer research: Past and present, Macromol. Rapid Comm, 24 (2003) 16–32.

[109]. Hoogenboom R, Schubert US, High-throughput synthesis equipment applied to polymer research, Rev. Sci. Instrum, 76 (2005) 1–7.

[110]. Anderson DG, Lynn DM, Langer R, Semi-automated synthesis and screening of a large library of degradable cationic polymers for gene delivery, Angew. Chem. Int. Ed, 42 (2003) 3153–3158.

[111]. Anderson DG, Akinc A, Hossain N, Langer R, Structure/property studies of polymeric gene delivery using a library of poly(beta-amino esters), Mol. Ther, 11 (2005) 426–434. [PubMed: 15727939]

[112]. Krska SW, DiRocco DA, Dreher SD, Shevlin M, The Evolution of Chemical High-Throughput Experimentation To Address Challenging Problems in Pharmaceutical Synthesis, Accounts Chem. Res, 50(2017)2976–2985.

[113]. Bedard AC, Adamo A, Aroh KC, Russell MG, Bedermann AA, Torosian J, Yue B, Jensen KF, Jamison TF, Reconfigurable system for automated optimization of diverse chemical reactions, Science, 361 (2018) 1220–1225. [PubMed: 30237351]

[114]. Paulus RM, Fitjen MW, de la Mar MJ, Hoogenboom R, Schubert US, Reversible Addition-Fragmentation Chain Transfer Polymerization on different Synthesizer Platforms, QSAR Comb. Sci, 24 (2005) 863–867.

[115]. Chan-Seng D, Zamfir M, Lutz JF, Polymer-Chain Encoding: Synthesis of Highly Complex Monomer Sequence Patterns by Using Automated Protocols, Angew. Chem. Int. Ed, 51 (2012) 12254–12257.

[116]. Fournier D, Hoogenboom R, Thijs HM, Paulus RM, Schubert US, Tunable pH- and Temperature-Sensitive Copolymer Libraries by Reversible Addition–Fragmentation Chain Transfer Copolymerizations of Methacrylates, Macromolecules, 40 (2007) 915–920.

[117]. Guerrero-Sanchez C, Harrisson S, Keddie DJ, High-Throughput Method for RAFT Kinetic Investigations and Estimation of Reactivity Ratios in Copolymerization Systems, Macromol. Symp, 325-326 (2013) 38–46.

[118]. Zhang H, Fitjen MW, Hoogenboom R, Reinierkens R, Schubert US, Application of a Parallel Synthetic Approach in Atom-Transfer Radical Polymerization: Set-Up and Feasibility Demonstration, Macromol. Rapid Comm, 24 (2003) 81–86.

[119]. Roy A, High Throughput Screening Operations at the University of Kansas, Comb. Chem. High Throughput Screen, 17 (2014) 387–393. [PubMed: 24661207]

[120]. Zolotaijova NI, Wynn R, Binding Assays for Bromodomain Proteins: Their Utility in Drug Discovery in Oncology and Inflammatory Disease, Curr. Protoc. Pharmacol, 80 (2018) 3–16.

[121]. Zucchelli P, Horak G, Jordan A, Devices and methods for programmable manipulation of pipettes, USPTO, (2018) 1–12.

[122]. Warhurst J, Nelson G, Cote R, Manually directed, multi-channel electronic pipetting system, USPTO, (2013) 1–16.

[123]. Sykes DA, Charlton SJ, Single Step Determination of Unlabeled Compound Kinetics Using a Competition Association Binding Method Employing Time-Resolved FRET, Rational Drug Design, 1824 (2018) 177–194.

[124]. Mattheakis L, Screening robotics and automation, J. Biomol. Screen, 19 (2014) 478–480. [PubMed: 24509067]

[125]. Ozgul S, von Daake S, Kakehi S, Sereni D, Denissova N, Hanlon C, Huang YJ, Everett JK, Yin CF, Montelione GT, Comoletti D, An ELISA-Based Screening Platform for Ligand-Receptor Discovery, Method Enzymol, 615 (2019) 453–475.

[126]. Olsen KN, Ask KS, Pedersen-Bjergaard S, Gjelstad A, Parallel artificial liquid membrane extraction of psychoactive analytes: a novel approach in therapeutic drug monitoring, Bioanalysis, 10 (2018) 385–395. [PubMed: 29451001]

[127]. Abdulla MH, Ruelas DS, Wolff B, Snedecor J, Lim KC, Xu FY, Renslo AR, Williams J, McKerrow JH, Caffrey CR, Drug Discovery for Schistosomiasis: Hit and Lead Compounds Identified in a Library of Known Drugs by Medium-Throughput Phenotypic Screening, PLoS Negl. Trop. Dis, 3 (2009) 1–14.

[128]. Guller R, Munch S, Gees T, Tschirky H, Device for conducting plurality of chemical, biochemical or physical procedures in parallel, USPTO, (2003) 1–10.

[129]. Rosso V, Albrecht J, Roberts F, Janey JM, Uniting laboratory automation, DoE data, and modeling techniques to accelerate chemical process development, React. Chem. Eng, 4 (2019) 1646–1657.

[130]. Jessop-Fabre MM, Sonnenschein N, Improving Reproducibility in Synthetic Biology, Front. Bioeng. Biotech, 7 (2019) 18.

[131]. Wang J, Deng K, Zhou C, Fang Z, Meyer C, Deshpande KU, Li Z, Mi X, Luo Q, Hammock BD, Tan C, Chen Y, Pan T, Microfluidic cap-to-dispense (mu CD): a universal microfluidic-robotic interface for automated pipette-free high-precision liquid handling, Lab Chip, 19 (2019) 3405–3415. [PubMed: 31501848]

[132]. Poulsen KM, Pho T, Champion JA, Payne CK, Automation and low-cost proteomics for characterization of the protein corona: experimental methods for big data, Anal. Bioanal. Chem, 412 (2020) 6543–6551. [PubMed: 32500258]

[133]. Christensen M, Adedeji F, Grosser S, Zawatzky K, Ji Y, Liu J, Jurica JA, Naber JR, Hein JE, Development of an automated kinetic profiling system with online HPLC for reaction optimization, React. Chem. Eng, 4 (2019) 1555–1558.

[134]. Yang S, Evans JRG, Metering and dispensing of powder; the quest for new solid freeforming techniques, Powder Technol, 178 (2007) 56–72.

[135]. Russell AJ, Baker SL, Colina CM, Figg CA, Kaar JL, Matyjaszewski K, Simakova A, Sumerlin BS, Next Generation of Protein-Polymer Conjugates, AIChe J, 64 (2018) 3230–3245.

[136]. Mattrey FT, Makarov AA, Regalado EL, Bernardoni F, Figus M, Hicks MB, Zheng JJ, Wang L, Schafer W, Antonucci V, Hamilton SE, Zawatzky K, Welch CJ, Current challenges and future prospects in chromatographic method development for pharmaceutical research, Trac-Trend Anal Chem, 95 (2017) 36–46.

[137]. Prabhu GRD, Urban PL, The dawn of unmanned analytical laboratories, TrAC Trends in Analytical Chemistry, 88 (2017) 41–52.

[138]. Welch CJ, Sajonz P, Biba M, Gouker J, Fairchild J, Comparison of Multiparallel Microfluidic HPLC Instruments for High Throughput Analyses in Support of Pharmaceutical Process Research, Journal of Liquid Chromatography & Related Technologies, 29 (2006) 2185–2200.

[139]. Yennawar NH, Fecko JA, Showalter SA, Bevilacqua PC, A High-Throughput Biological Calorimetry Core: Steps to Startup, Run, and Maintain a Multiuser Facility, Calorimetry, 567 (2016) 435–460.

[140]. Shi RH, Chandra D, Chien WM, Wang JJ, High-throughput thermodynamic computation and experimental study of solid-state phase transitions in organic multicomponent orientationally disordered phase change materials for thermal energy storage, Calphad, 64 (2019) 66–77.

[141]. Thuriot-Roukos J, Bennis M, Heuson E, Roussel P, Dumeignil F, Paul S, Design of a multi-well plate for high-throughput characterization of heterogenous catalysts by XRD, FT-IR, Raman, and XRF spectroscopies, RSC Adv, 8 (2018) 40912–40920.

[142]. Chiang PC, Ran YQ, Chou KJ, Cui Y, Sambrone A, Chan CN, Hart R, Evaluation of Drug Foad and Polymer by Using a 96-Well Plate Vacuum Dry System for Amorphous Solid Dispersion Drug Delivery, AAPS Pharmscitech, 13 (2012) 713–722. [PubMed: 22562615]

[143]. Mohr J, Chuan YP, Wu Y, Lua LH, Middelberg AP, Virus-like particle formulation optimization by miniaturized high-throughput screening, Methods, 60 (2013) 248–256. [PubMed: 23639868]

[144]. He F, Woods CE, Becker GW, Narhi FO, Razinkov VI, High-throughput assessment of thermal and colloidal stability parameters for monoclonal antibody formulations, J. Pharm. Sci, 100 (2011) 5126–5141. [PubMed: 21789772]

[145]. Sun H, Choi W, Zang N, Battistella C, Thompson MP, Cao W, Zhou X, Forman C, Gianneschi NC, Bioactive Peptide Brush Polymers via Photoinduced Reversible-Deactivation Radical Polymerization, Angew. Chem. Int. Ed, 58 (2019) 17359–17364.

[146]. Ferguson AF, Machine learning and data science in soft materials engineering, J. Phys. Condens. Matter, 30(2018) 043002. [PubMed: 29111979]

[147]. Jackson NE, Webb MA, de Pablo JJ, Recent advances in machine learning towards multiscale soft materials design, Curr. Opin. Chem. Eng, 23 (2019) 106–114.

[148]. Audus DJ, de Pablo JJ, Polymer Informatics: Opportunities and Challenges, ACS Macro Lett, 6 (2017)1078–1082. [PubMed: 29201535]

[149]. de Pablo JJ, Jackson NE, Webb MA, Chen F, Moore JE, Morgan D, Jacobs R, Pollock T, Schlom DG, Toberer ES, Analytis J, Dabo I, DeLongchamp DM, Fiete GA, Grason GM, Hautier G, Mo Y, Rajan K, Reed EJ, Rodriguez E, Stevanovic V, Suntivich J, Thornton K, Zhao J J, New frontiers for the materials genome initiative, NPJ Comput. Mater, 5 (2019) 1–23.

[150]. Ash S, Cline MA, Homer RW, Hurst T, Smith GB, SYBYF Fine Notation (SEN): A Versatile Fanguage for Chemical Structure Representation, J. Chem. Inf. Comp. Sci, 37 (1997) 71–79.

[151]. Zhang T, Li H, Xi H, Stanton RV, Rotstein SH, HELM: a hierarchical notation language for complex biomolecule structure representation, J. Chem. Inf. Model, 52 (2012) 2796–2806. [PubMed: 22947017]

[152]. Drefahl A, CurlySMILES: a chemical language to customize and annotate encodings of molecular and nanodevice structures, J. Cheminformatics, 3 (2011) 1.

[153]. Lin TS, Coley CW, Mochigase H, Beech HK, Wang WC, Wang Z, Woods E, Craig SL, Johnson JA, Kalow JA, Jensen KF, Olsen BD, BigSMIFES: A Structurally-Based Fine Notation for Describing Macromolecules, ACS Cent. Sci, 5 (2019) 1523–1531. [PubMed: 31572779]

[154]. Kutchukian PS, Vasilyeva NY, Xu J, Findvall MK, Dillon MP, Glick M, Coley JD, Brooijmans N, Inside the Mind of a Medicinal Chemist: The Role of Human Bias in Compound Prioritization during Drug Discovery, PLOS ONE, 7 (2012) e48476. [PubMed: 23185259]

[155]. Schnecke V, Bostrom J, Computational chemistry-driven decision making in lead generation, Drug Discov. Today, 11 (2006) 43–50. [PubMed: 16478690]

[156]. Das P, Moll M, Stamati H, Kavraki LE, Clementi C, Low-dimensional, free-energy landscapes of protein-folding reactions by nonlinear dimensionality reduction, Proc. Natl. Acad. Sci. U.S.A, 103 (2006) 9885–9890. [PubMed: 16785435]

[157]. Ferguson AL, Zhang S, Dikiy I, Panagiotopoulos AZ, Debenedetti PG, James Link A, An experimental and computational investigation of spontaneous lasso formation in microcin J25, Biophys. J, 99 (2010) 3056–3065. [PubMed: 21044604]

[158]. Warren DB, Bergström CAS, Benameur H, Porter CJH, Pouton CW, Evaluation of the Structural Determinants of Polymeric Precipitation Inhibitors Using Solvent Shift Methods and Principle Component Analysis, Mol. Pharm, 10 (2013) 2823–2848. [PubMed: 23631696]

[159]. Bishop CJ, Abubaker-Sharif B, Guiriba T, Tzeng SY, Green JJ, Gene delivery polymer structure-function relationships elucidated via principal component analysis, ChemComm, 51 (2015) 12134–12137.

[160]. MacCuish JD, MacCuish NE, Chemoinformatics applications of cluster analysis, Wiley Interdiscip. Rev. Comput. Mol. Sci, 4 (2014) 34–48.

[161]. Tavazoie S, Hughes JD, Campbell MJ, Cho RJ, Church GM, Systematic determination of genetic network architecture, Nat. Genet, 22 (1999) 281–285. [PubMed: 10391217]

[162]. Bicerano J, Prediction of polymer properties, Marcel Dekker, New York, 1993.

[163]. Ramprasad R, Batra R, Pilania G, Mannodi-Kanakkithodi A, Kim C, Machine learning in materials informatics: recent applications and prospects, Npj Comput. Mater, 3 (2017).

[164]. Zhou T, Song Z, Sundmacher K, Big Data Creates New Opportunities for Materials Research: A Review on Methods and Applications of Machine Learning for Materials Design, Engineering, 5 (2019) 1017–1026.

[165]. Mannodi-Kanakkithodi A, Pilania G, Huan TD, Lookman T, Ramprasad R, Machine Learning Strategy for Accelerated Design of Polymer Dielectrics, Sci. Rep, 6 (2016) 20952. [PubMed: 26876223]

[166]. Kim C, Chandrasekaran A, Jha A, Ramprasad R, Active-learning and materials design: the example of high glass transition temperature polymers, MRS Commun, 9 (2019) 860–866.

[167]. Khan PM, Rasulev B, Roy K, QSPR Modeling of the Refractive Index for Diverse Polymers Using 2D Descriptors, ACS Omega, 3 (2018) 13374–13386. [PubMed: 31458051]

[168]. Shmilovich K, Mansbach RA, Sidky H, Dunne OE, Panda SS, Tovar JD, Ferguson AL, Discovery of Self-Assembling pi-Conjugated Peptides by Active Learning-Directed Coarse-Grained Molecular Simulation, J. Phys. Chem. B, 124 (2020) 3873–3891. [PubMed: 32180410]

[169]. Wang Y, Xie T, France-Lanord A, Berkley A, Johnson JA, Shao-Horn Y, Grossman JC, Toward Designing Highly Conductive Polymer Electrolytes by Machine Learning Assisted Coarse-Grained Molecular Dynamics, Chem. Mater, 32 (2020) 4144–4151.

[170]. Nagasawa S, Al-Naamani E, Saeki A, Computer-Aided Screening of Conjugated Polymers for Organic Solar Cell: Classification by Random Forest, J. Phys. Chem. Lett, 9 (2018) 2639–2646. [PubMed: 29733216]

[171]. Reker D, Schneider G, Active-learning strategies in computer-assisted drug discovery, Drug Discov. Today, 20 (2015) 458–465. [PubMed: 25499665]

[172]. Schneider G, Schuller A, Adaptive combinatorial design of focused compound libraries, Methods Mol. Biol, 572 (2009) 135–147. [PubMed: 20694689]

[173]. Schneider G, Hartenfeller M, Reutlinger M, Tanrikulu Y, Proschak E, Schneider P, Voyages to the (un)known: adaptive design of bioactive compounds, Trends Biotechnol, 27 (2009) 18–26. [PubMed: 19004513]

[174]. Ruipérez F, Application of quantum chemical methods in polymer chemistry, Int. Rev. Phys. Chem, 38 (2019) 343–403.

[175]. Gartner TE, Jayaraman A, Modeling and Simulations of Polymers: A Roadmap, Macromolecules, 52 (2019) 755–786.

[176]. Iovanac NC, Savoie BM, Improved Chemical Prediction from Scarce Data Sets via Latent Space Enrichment, J. Phys. Chem. A, 123 (2019) 4295–4302. [PubMed: 31032614]

[177]. Cai C, Wang S, Xu Y, Zhang W, Tang K, Ouyang Q, Lai L, Pei J, Transfer Learning for Drug Discovery, J. Med. Chem, 63 (2020) 8683–8694. [PubMed: 32672961]

[178]. Doerr S, Harvey MJ, Noe F, De Fabritiis G, HTMD: High-Throughput Molecular Dynamics for Molecular Discovery, J. Chem. Theory Comput, 12 (2016) 1845–1852. [PubMed: 26949976]

[179]. Schneider G, Virtual screening: an endless staircase?, Nat. Rev. Drug Discov, 9 (2010) 273–276. [PubMed: 20357802]

[180]. Wang Z, Sun H, Shen C, Hu X, Gao J, Li D, Cao D, Hou T, Combined strategies in structure-based virtual screening, Phys. Chem. Chem. Phys, 22 (2020) 3149–3159. [PubMed: 31995074]

[181]. Webb MA, Savoie BM, Wang Z, Miller TF III, Chemically Specific Dynamic Bond Percolation Model for Ion Transport in Polymer Electrolytes, Macromolecules, 48 (2015) 7346–7358.

[182]. Grunewald F, Rossi G, de Vries AH, Marrink SJ, Monticelli L, Transferable MARTINI Model of Poly(ethylene Oxide), J. Phys. Chem. B, 122 (2018) 7436–7449. [PubMed: 29966087]

[183]. Rossi G, Monticelli L, Puisto SR, Vattulainen I, Ala-Nissila T, Coarse-graining polymers with the MARTINI force-field: polystyrene as a benchmark case, Soft Matter, 7 (2011) 698–708.

[184]. Carbone P, Varzaneh HAK, Chen XY, Muller-Plathe F, Transferability of coarse-grained force fields: The polymer case, J. Chem. Phys, 128 (2008) 064904. [PubMed: 18282071]

[185]. Bayramoglu B, Faller R, Coarse-Grained Modeling of Polystyrene in Various Environments by Iterative Boltzmann Inversion, Macromolecules, 45 (2012) 9205–9219.

[186]. Izvekov S, Voth GA, A multiscale coarse-graining method for biomolecular systems, J. Phys. Chem. B, 109 (2005) 2469–2473. [PubMed: 16851243]

[187]. Ruhle V, Junghans C, Lukyanov A, Kremer K, Andrienko D, Versatile Object-Oriented Toolkit for Coarse-Graining Applications, J. Chem. Theory Comput, 5 (2009) 3211–3223. [PubMed: 26602505]

[188]. Dunn NJH, Lebold KM, DeLyser MR, Rudzinski JF, Noid WG, BOCS: Bottom-up Open-source Coarse-graining Software, J. Phys. Chem. B, 122 (2018) 3363–3377. [PubMed: 29227668]

[189]. Wang W, Gómez-Bombarelli R, Coarse-graining auto-encoders for molecular dynamics, Npj Comput. Mater, 5 (2019) 1–9.

[190]. Webb MA, Delannoy JY, de Pablo JJ, Graph-Based Approach to Systematic Molecular Coarse-Graining, J. Chem. Theory Comput, 15 (2019) 1199–1208. [PubMed: 30557028]

[191]. Li Z, Wellawatte GP, Chakraborty M, Gandhi HA, Xu C, White AD, Graph neural network based coarse-grained mapping prediction, Chem. Sci, 11 (2020) 9524–9531.

[192]. Chakraborty M, Xu C, White AD, Encoding and selecting coarse-grain mapping operators with hierarchical graphs, J. Chem. Phys, 149 (2018) 134106. [PubMed: 30292213]

[193]. Hung CL, Gonzalez-Tudela A, Cirac JI, Kimble HJ, Quantum spin dynamics with pairwise-tunable, long-range interactions, Proc. Natl. Acad. Sci, 113 (2016) E4946–4955. [PubMed: 27496329]

[194]. Sherman ZM, Howard MP, Lindquist BA, Jadrich RB, Truskett TM, Inverse methods for design of soft materials, J. Chem. Phys, 152 (2020) 140902. [PubMed: 32295358]

[195]. Gómez-Bombarelli R, Wei JN, Duvenaud D, Hernández-Lobato JM, Sánchez-Lengeling B, Sheberla D, Aguilera-Iparraguirre J, Hirzel TD, Adams RP, Aspuru-Guzik A, Automatic Chemical Design Using a Data-Driven Continuous Representation of Molecules, ACS Cent. Sci, 4 (2018) 268–276. [PubMed: 29532027]

[196]. Khadilkar MR, Paradiso S, Delaney KT, Fredrickson GHJM, Inverse design of bulk morphologies in multiblock polymers using particle swarm optimization, Macromolecule, 50 (2017) 6702–6709.

[197]. Yichi Z, Apley DW, Chen W, Bayesian Optimization for Materials Design with Mixed Quantitative and Qualitative Variables, Sci. Rep, 10 (2020) 1–13. [PubMed: 31913322]

[198]. Medina E, Pieper DH, Tackling Threats and Future Problems of Multidrug-Resistant Bacteria, Curr. Top. Microbiol, 398 (2016) 3–33.

[199]. Mocan L, Tabaran FA, Mocan T, Pop T, Mosteanu O, Agoston-Coldea L, Matea CT, Gonciar D, Zdrehus C, Iancu C, Laser thermal ablation of multidrug-resistant bacteria using functionalized gold nanoparticles, Int. J. Nanomed, 12 (2017) 2255–2263.

[200]. Wu XZ, Li Z, Li XL, Tian YM, Fan YZ, Yu CH, Zhou BL, Liu Y, Xiang R, Yang L, Synergistic effects of antimicrobial peptide DP7 combined with antibiotics against multidrug-resistant bacteria, Drug Des. Dev. Ther, 11 (2017) 939–946.

[201]. Glatzel S, Hezwani M, Kitson PJ, Gromski PS, Schurer S, Cronin L, A Portable 3D Printer System for the Diagnosis and Treatment of Multidrug-Resistant Bacteria, Chem-Us, 1 (2016) 494–504.

[202]. Riley MMS, The Rising Problem of Multidrug-Resistant Organisms in Intensive Care Units, Crit. Care Nurse, 39 (2019) 48–55. [PubMed: 31371367]

[203]. Nguyen TK, Lam SJ, Ho KKK, Kumar N, Qiao GG, Egan S, Boyer C, Wong EHH, Rational Design of Single-Chain Polymeric Nanoparticles That Kill Planktonic and Biofilm Bacteria, ACS Infect. Dis, 3 (2017) 237–248. [PubMed: 28135798]

[204]. Lam SJ, Wong EHH, Boyer C, Qiao GG, Antimicrobial polymeric nanoparticles, Prog. Polym. Sci, 76 (2018) 40–64.

[205]. Judzewitsch PR, Nguyen TK, Shanmugam S, Wong EHH, Boyer C, Towards Sequence-Controlled Antimicrobial Polymers: Effect of Polymer Block Order on Antimicrobial Activity, Angew. Chem. Int. Ed, 57 (2018) 4559–4564.

[206]. Judzewitsch PR, Zhao L, Wong EHH, Boyer C, High-Throughput Synthesis of Antimicrobial Copolymers and Rapid Evaluation of Their Bioactivity, Macromolecules, 52 (2019) 3975–3986.

[207]. Judzewitsch PR, Corrigan N, Trujillo F, Xu J, Moad G, Hawker CJ, Wong EHH, Boyer C, High-Throughput Process for the Discovery of Antimicrobial Polymers and Their Upscaled Production via Flow, Macromolecules, 53 (2020) 631–639.

[208]. Richards SJ, Isufi K, Wilkins LE, Lipecki J, Fullam E, Gibson MI, Multivalent Antimicrobial Polymer Nanoparticles Target Mycobacteria and Gram-Negative Bacteria by Distinct Mechanisms, Biomacromolecules, 19 (2018) 256–264. [PubMed: 29195272]

[209]. Wang J, Rivero M, Bonilla AM, Sanchez-Marcos J, Xue WT, Chen GJ, Zhang WD, Zhu XL, Natural RAFT Polymerization: Recyclable-Catalyst-Aided, Opened-to Air, and Sunlight-Photolyzed RAFT Polymerizations, ACS Macro. Lett, 5 (2016) 1278–1282.

[210]. Zheng Y, Luo Y, Feng K, Zhang W, Chen G, High Throughput Screening of Glycopolymers: Balance between Cytotoxicity and Antibacterial Property, ACS Macro Lett, 8 (2019) 326–330.

[211]. Fu Q, Xie K, McKenzie TG, Qiao GG, Trithiocarbonates as intrinsic photoredox catalysts and RAFT agents for oxygen tolerant controlled radical polymerization, Polym. Chem, 8 (2017) 1519–1526.

[212]. Sun H, Yang L, Thompson MP, Schara S, Cao W, Choi W, Hu ZY, Zang NZ, Tan WH, Gianneschi NC, Recent Advances in Amphiphilic Polymer-Oligonucleotide Nanomaterials via Living/Controlled Polymerization Technologies, Bioconjug. Chem, 30 (2019) 1889–1904. [PubMed: 30969752]

[213]. Lueckheide M, Vieregg JR, Bologna AJ, Leon L, Tirrell MV, Structure-Property Relationships of Oligonucleotide Polyelectrolyte Complex Micelles, Nano Lett, 18 (2018) 7111–7117. [PubMed: 30339032]

[214]. Marras AE, Vieregg JR, Ting JM, Rubien JD, Tirrell MV, Polyelectrolyte Complexation of Oligonucleotides by Charged Hydrophobic-Neutral Hydrophilic Block Copolymers, Polymers, 11 (2019)83.

[215]. Green JJ, Zugates GT, Tedford NC, Huang YH, Griffith LG, Lauffenburger DA, Sawicki JA, Langer R, Anderson DG, Combinatorial modification of degradable polymers enables transfection of human cells comparable to adenovirus, Adv. Mater, 19 (2007) 2836–2842.

[216]. Green JJ, Langer R, Anderson DG, A combinatorial polymer library approach yields insight into nonviral gene delivery, Accounts Chem. Res, 41 (2008) 749–759.

[217]. Wilson DR, Rui Y, Siddiq K, Routkevitch D, Green JJ, Differentially Branched Ester Amine Quadpolymers with Amphiphilic and pH-Sensitive Properties for Efficient Plasmid DNA Delivery, Mol. Pharmaceut, 16 (2019) 655–668.

[218]. Yan HJ, Zhu DC, Zhou ZX, Liu X, Piao Y, Zhang Z, Liu XR, Tang JB, Shen YQ, Facile synthesis of semi-library of low charge density cationic polyesters from poly(alkylene maleate)s for efficient local gene delivery, Biomaterials, 178 (2018) 559–569. [PubMed: 29653872]

[219]. Ting JM, Nayale TS, Jones SD, Bates FS, Reineke TM, Deconstructing HPMCAS: Excipient Design to Tailor Polymer-Drug Interactions for Oral Drug Delivery, ACS Biomater. Sci. Eng, 1 (2015) 978–990. [PubMed: 33429529]

[220]. Ricarte RG, Van Zee NJ, Li Z, Johnson LM, Lodge TP, Hillmyer MA, Recent Advances in Understanding the Micro- and Nanoscale Phenomena of Amorphous Solid Dispersions, Mol. Pharmaceut, 16 (2019) 4089–4103.

[221]. Xiang TX, Anderson BD, Molecular Dynamics Simulation of Amorphous Hydroxypropyl-Methylcellulose Acetate Succinate (HPMCAS): Polymer Model Development, Water Distribution, and Plasticization, Mol. Pharmaceut, 11 (2014) 2400–2411.

[222]. Xiang TX, Anderson BD, Molecular Dynamics Simulation of Amorphous Hydroxypropylmethylcellulose and Its Mixtures With Felodipine and Water, J. Pharm. Sci, 106 (2017)803–816. [PubMed: 27986292]

[223]. Mandal T, Marson RL, Larson RG, Coarse-grained modeling of crystal growth and polymorphism of a model pharmaceutical molecule, Soft Matter, 12 (2016) 8246–8255. [PubMed: 27714373]

[224]. Mandal T, Huang WJ, Mecca JM, Getchell A, Porter WW, Larson RG, A framework for multi-scale simulation of crystal growth in the presence of polymers, Soft Matter, 13 (2017) 1904–1913. [PubMed: 28181622]

[225]. Frank DS, Zhu QY, Matzger AJ, Inhibiting or Accelerating Crystallization of Pharmaceuticals by Manipulating Polymer Solubility, Mol. Pharmaceut, 16 (2019) 3720–3725.

[226]. Tale S, Purchel AA, Dalsin MC, Reineke TM, Diblock Terpolymers Are Tunable and pH Responsive Vehicles To Increase Hydrophobic Drug Solubility for Oral Administration, Mol. Pharmaceut, 14 (2017) 4121–4127.

[227]. Johnson LM, Li Z, LaBelle AJ, Bates FS, Lodge TP, Hillmyer MA, Impact of Polymer Excipient Molar Mass and End Groups on Hydrophobic Drug Solubility Enhancement, Macromolecules, 50 (2017) 1102–1112.

[228]. Johnson LM, Hillmyer MA, Critical Excipient Properties for the Dissolution Enhancement of Phenytoin, ACS Omega, 4 (2019) 19116–19127. [PubMed: 31763534]

[229]. Tjandra KC, Thordarson P, Multivalency in Drug Delivery-When Is It Too Much of a Good Thing?, Bioconjug. Chem, 30 (2019) 503–514. [PubMed: 30742420]

[230]. Lynn GM, Chytil P, Francica JR, Lagova A, Kueberuwa G, Ishizuka AS, Zaidi N, Ramirez-Valdez RA, Blobel NJ, Baharom F, Leal J, Wang AQ, Gemer MY, Etrych T, Ulbrich K, Seymour LW, Seder RA, Laga R, Impact of Polymer-TLR-7/8 Agonist (Adjuvant) Morphology on the Potency and Mechanism of CD8 T Cell Induction, Biomacromolecules, 20 (2019) 854–870. [PubMed: 30608149]

[231]. Ryu KA, Slowinska K, Moore T, Esser-Kahn A, Immune Response Modulation of Conjugated Agonists with Changing Linker Length, ACS Chem. Biol, 11 (2016) 3347–3352. [PubMed: 27749034]

[232]. Martyn B, Biggs CI, Gibson MI, Comparison of systematically functionalized heterogeneous and homogenous glycopolymers as toxin inhibitors, J. Polym. Sci. Pol. Chem, 57 (2019) 40–47.

[233]. Wilkins LE, Badi N, Du Prez F, Gibson MI, Double-Modified Glycopolymers from Thiolactones to Modulate Lectin Selectivity and Affinity, ACS Macro Lett, 7 (2018) 1498–1502. [PubMed: 30662815]

[234]. Richards SJ, Baker AN, Walker M, Gibson MI, Polymer-Stabilized Sialylated Nanoparticles: Synthesis, Optimization, and Differential Binding to Influenza Hemagglutinins, Biomacromolecules, 21 (2020) 1604–1612. [PubMed: 32191036]

[235]. Georgiou PG, Baker AN, Richards SJ, Laezza A, Walker M, Gibson MI, Tuning aggregative versus non-aggregative lectin binding with glycosylated nanoparticles by the nature of the polymer ligand, J. Mater. Chem. B, 8 (2020) 136–145. [PubMed: 31778137]

[236]. Song Y, Moore EG, Guo Y, Moore JS, Polymer-Peptide Conjugates Disassemble Amyloid beta Fibrils in a Molecular-Weight Dependent Manner, J. Am. Chem. Soc, 139 (2017) 4298–4301. [PubMed: 28290684]

[237]. Song Y, Cheng PN, Zhu LJ, Moore EG, Moore JS, Multivalent Macromolecules Redirect Nucleation-Dependent Fibrillar Assembly into Discrete Nanostructures, J. Am. Chem. Soc, 136 (2014)5233–5236. [PubMed: 24661268]

[238]. Callmann CE, Thompson MP, Gianneschi NC, Poly(peptide): Synthesis, Structure, and Function of Peptide-Polymer Amphiphiles and Protein-like Polymers, Accounts Chem. Res, 53 (2020) 400–413.

[239]. Blum AP, Nelles DA, Hidalgo FJ, Touve MA, Sim DS, Madrigal AA, Yeo GW, Gianneschi NC, Peptide Brush Polymers for Efficient Delivery of a Gene Editing Protein to Stem Cells, Angew. Chem. Int. Ed, 58 (2019) 15646–15649.

[240]. Ku TH, Chien MP, Thompson MP, Sinkovits RS, Olson NH, Baker TS, Gianneschi NC, Controlling and Switching the Morphology of Micellar Nanoparticles with Enzymes, J. Am. Chem. Soc, 133 (2011) 8392–8395. [PubMed: 21462979]

[241]. Chien MP, Carlini AS, Hu DH, Barback CV, Rush AM, Hall DJ, Orr G, Gianneschi NC, Enzyme-Directed Assembly of Nanoparticles in Tumors Monitored by in Vivo Whole Animal Imaging and ex Vivo Super-Resolution Fluorescence Imaging, J. Am. Chem. Soc, 135 (2013) 18710–18713. [PubMed: 24308273]

[242]. Nguyen MM, Carlini AS, Chien MP, Sonnenberg S, Luo CL, Braden RL, Osborn KG, Li YW, Gianneschi NC, Christman KL, Enzyme-Responsive Nanoparticles for Targeted Accumulation and Prolonged Retention in Heart Tissue after Myocardial Infarction, Adv. Mater, 27 (2015) 5547–5552. [PubMed: 26305446]

[243]. Ungerleider JL, Kammeyer JK, Braden RL, Christman KL, Gianneschi NC, Enzyme-Targeted Nanoparticles for Delivery to Ischemic Skeletal Muscle, Polym. Chem, 8 (2017) 5212–5219. [PubMed: 29098018]

[244]. Callmann CE, Barback CV, Thompson MP, Hall DJ, Mattrey RF, Gianneschi NC, Therapeutic Enzyme-Responsive Nanoparticles for Targeted Delivery and Accumulation in Tumors, Adv. Mater, 27 (2015) 4611–4615. [PubMed: 26178920]

[245]. Mannodi-Kanakkithodi A, Pilania G, Huan TD, Lookman T, Ramprasad R, Machine Learning Strategy for Accelerated Design of Polymer Dielectrics, Sci. Rep, 6 (2016) 20952. [PubMed: 26876223]

[246]. Fiten MWM, Paulus RM, Schubert US, Systematic parallel investigation of RAFT polymerizations for eight different (meth)acrylates: A basis for the designed synthesis of block and random copolymers, J. Polym. Sci. A Polym. Chem, 43 (2005) 3831–3839.

[247]. Kholodovych V, Gubskaya AV, Bohrer M, Harris N, Knight D, Kohn J, Welsh WJ, Prediction of biological response for large combinatorial libraries of biodegradable polymers: Polymethacrylates as a test case, Polymer, 49 (2008) 2435–2439.

[248]. Smith JR, Kholodovych V, Knight D, Kohn J, Welsh WJ, Predicting fibrinogen adsorption to polymeric surfaces in silico: a combined method approach, Polymer, 46 (2005) 4296–4306.

[249]. Kholodovych V, Smith JR, Knight D, Abramson S, Kohn J, Welsh WJ, Accurate predictions of cellular response using QSPR: a feasibility test of rational design of polymeric biomaterials, Polymer, 45 (2004) 7367–7379.

[250]. Wu S, Kondo Y, Kakimoto MA, Yang B, Yamada H, Kuwajima I, Lambard G, Hongo K, Xu YB, Shiomi J, Schick C, Morikawa J, Yoshida R, Machine-learning-assisted discovery of polymers with high thermal conductivity using a molecular design algorithm, Npj Comput. Mater, 5 (2019) 1–11.

[251]. Huan TD, Mannodi-Kanakkithodi A, Ramprasad R, Accelerated materials property predictions and design using motif-based fingerprints, Phys. Rev. B, 92 (2015) 1–10.

[252]. Pilania G, Wang CC, Jiang X, Rajasekaran S, Ramprasad R, Accelerating materials property predictions using machine learning, Sci. Rep, 3 (2013) 1–6.

[253]. Mohammadi Y, Saeb MR, Penlidis A, Jabbari E, Stadler FJ, Zinck P, Matyjaszewski K, Intelligent Machine Learning: Tailor-Making Macromolecules, Polymers, 11 (2019) 579.

[254]. Bejagam KK, An YX, Singh S, Deshmukh SA, Machine-Learning Enabled New Insights into the Coil-to-Globule Transition of Thermosensitive Polymers Using a Coarse-Grained Model, J. Phys. Chem. Lett, 9 (2018) 6480–6488. [PubMed: 30372083]

[255]. Wei Q, Melko RG, Chen JZY, Identifying polymer states by machine learning, Phys. Rev. E, 95 (2017) 032504. [PubMed: 28415199]

[256]. Wang J, Olsson S, Wehmeyer C, Perez A, Charron NE, de Fabritiis G, Noe F, Clementi C, Machine Learning of Coarse-Grained Molecular Dynamics Force Fields, ACS Cent. Sci, 5 (2019) 755–767. [PubMed: 31139712]

[257]. Jackson NE, Bowen AS, Antony LW, Webb MA, Vishwanath V, de Pablo JJ, Electronic structure at coarse-grained resolutions from supervised machine learning, Sci. Adv, 5 (2019) 1–10.

[258]. Steiner S, Wolf J, Glatzel S, Andreou A, Granda JM, Keenan G, Hinkley T, Aragon-Camarasa G, Kitson PJ, Angelone D, Cronin L, Organic synthesis in a modular robotic system driven by a chemical programming language, Science, 363 (2019) 1–8.

[259]. Coley CW, Thomas DA III, Lummiss JAM, Jaworski JN, Breen CP, Schultz V, Hart T, Fishman JS, Rogers L, Gao HY, Hicklin RW, Plehiers PP, Byington J, Piotti JS, Green WH, Hart AJ, Jamison TF, Jensen KF, A robotic platform for flow synthesis of organic compounds informed by AI planning, Science, 365 (2019) 557–565.

[260]. Coley CW, Barzilay R, Jaakkola TS, Green WH, Jensen KF, Prediction of Organic Reaction Outcomes Using Machine Learning, ACS Cent. Sci, 3 (2017) 434–443. [PubMed: 28573205]

[261]. Coley CW, Green WH, Jensen KF, Machine Learning in Computer-Aided Synthesis Planning, Accounts Chem. Res, 51 (2018) 1281–1289.

[262]. Coley CW, Jin WG, Rogers L, Jamison TF, Jaakkola TS, Green WH, Barzilay R, Jensen KF, A graph-convolutional neural network model for the prediction of chemical reactivity, Chem. Sci, 10 (2019) 370–377. [PubMed: 30746086]

[263]. Machillot P, Quintal C, Dalonneau F, Hermant L, Monnot P, Matthews K, Fitzpatrick V, Liu J, Pignot-Paintrand I, Picart C, Automated Buildup of Biomimetic Films in Cell Culture Microplates for High-Throughput Screening of Cellular Behaviors, Adv. Mater, 30 (2018) 1801097.

[264]. Repin M, Pampou S, Karan C, Brenner DJ, Garty G, RABiT-II: Implementation of a High-Throughput Micronucleus Biodosimetry Assay on Commercial Biotech Robotic Systems, Radiat. Res, 187 (2017) 492–498. [PubMed: 28231025]

[265]. Pushpakom S, Iorio F, Eyers PA, Escott KJ, Hopper S, Wells A, Doig A, Guilliams T, Latimer J, McNamee C, Norris A, Sanseau P, Cavalla D, Pirmohamed M, Drug repurposing: progress, challenges and recommendations, Nat. Rev. Drug Discov, 18 (2018) 41–58. [PubMed: 30310233]

[266]. Waring MJ, Arrowsmith J, Leach AR, Leeson PD, Mandrell S, Owen RM, Pairaudeau G, Pennie WD, Pickett SD, Wang J, Wallace O, Weir A, An analysis of the attrition of drug candidates from four major pharmaceutical companies, Nat. Rev. Drug Discov, 14 (2015) 475–486. [PubMed: 26091267]

[267]. Pammolli F, Magazzini L, Riccaboni M, The productivity crisis in pharmaceutical R&D, Nat. Rev. Drug Discov, 10 (2011) 428–438. [PubMed: 21629293]

[268]. Auch C, Harms M, Mäder K, How changes in molecular weight and PDI of a polymer in amorphous solid dispersions impacts dissolution performance, Int. J. Pharm, 556 (2019) 372–382. [PubMed: 30553957]

[269]. Weininger D, SMILES, a Chemical Language and Information System. 1. Introduction to Methodology and Encoding Rules, J. Chem. Inf. Comp. Sci, 28 (1988) 31–36.

[270]. Weininger D, Weininger A, Weininger JL, SMILES. 2. Algorithm for Generation of Unique SMILES Notation, J Chem Inf Comp Sci, 29 (1989) 97–101.

[271]. Kim D, Oh PY, Lab automation drones for mobile manipulation in high throughput systems, 2018 IEEE International Conference on Consumer Electronics (ICCE), (2018) 1–5.

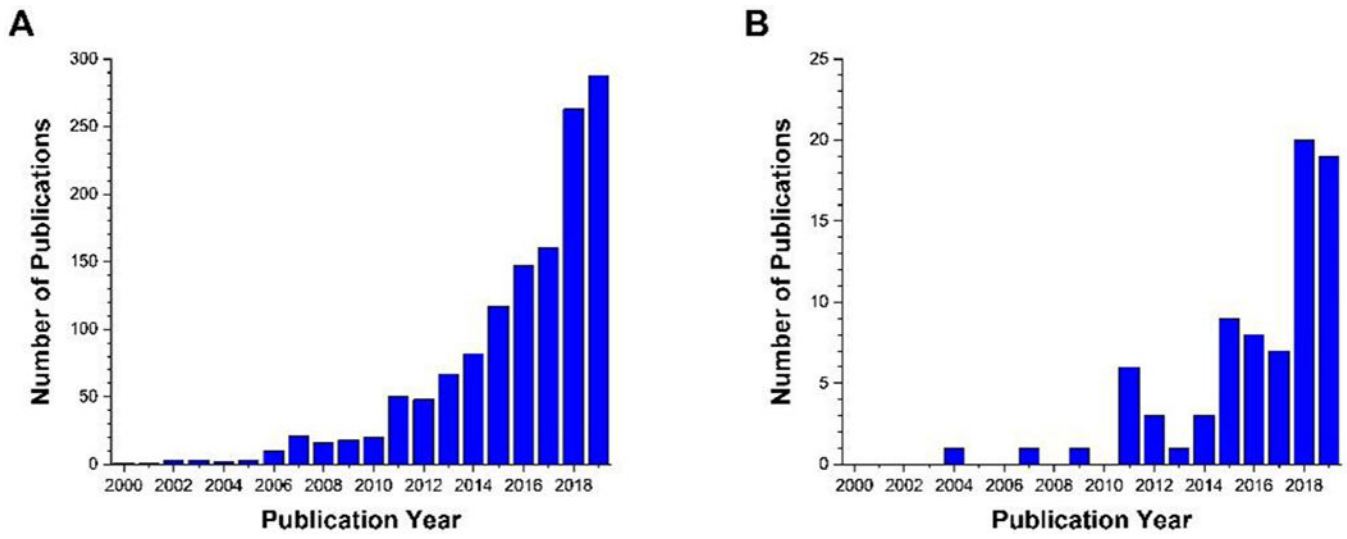


Fig. 1.

PubMed hits for peer-reviewed publications involving ML, AI, pharmaceuticals, and drug delivery over the period from 2000-2019. (**A**) Number of publications from 2000-2019 containing “machine learning,” “artificial intelligence,” and “pharmaceutical.” (**B**) Number of publications from 2000-2019 containing “machine learning,” “artificial intelligence,” and “drug delivery.”

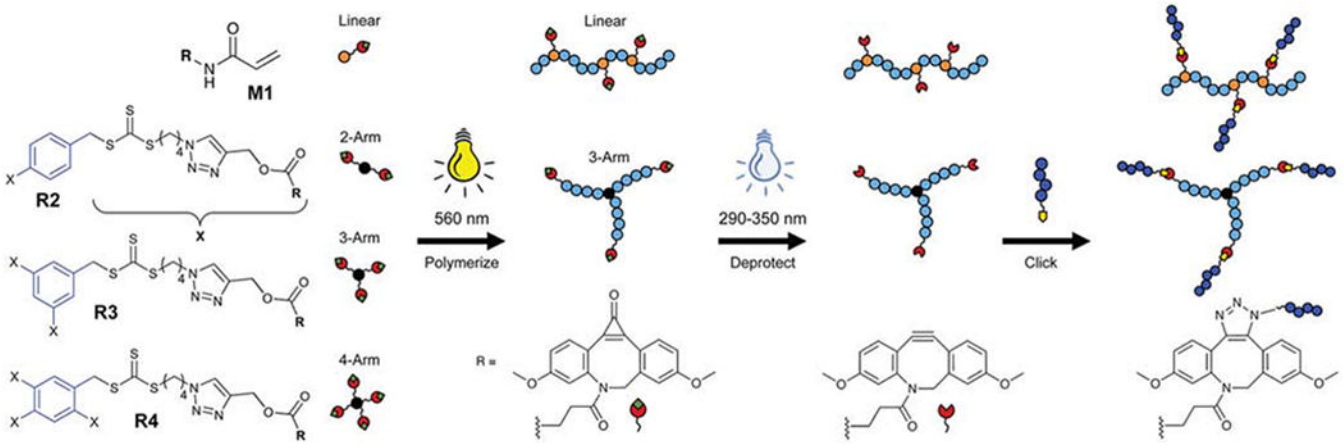


Fig. 2.

Various bioactive polymer architectures are possible in high throughput using cp-DIBAC. Linear functional polymers can be synthesized by polymerizing cp-DIBAC monomer (**M1**) onto the polymer backbone. End-functionalized 2-arm, 3-arm, and 4-arm polymers can also be synthesized by utilizing respective RAFT agents (**R2**, **R3**, and **R4**). Deprotection is conducted at 290-350 nm prior to clicking ligand. Reprinted with permission from the American Chemical Society. Copyright 2019 American Chemical Society [20].

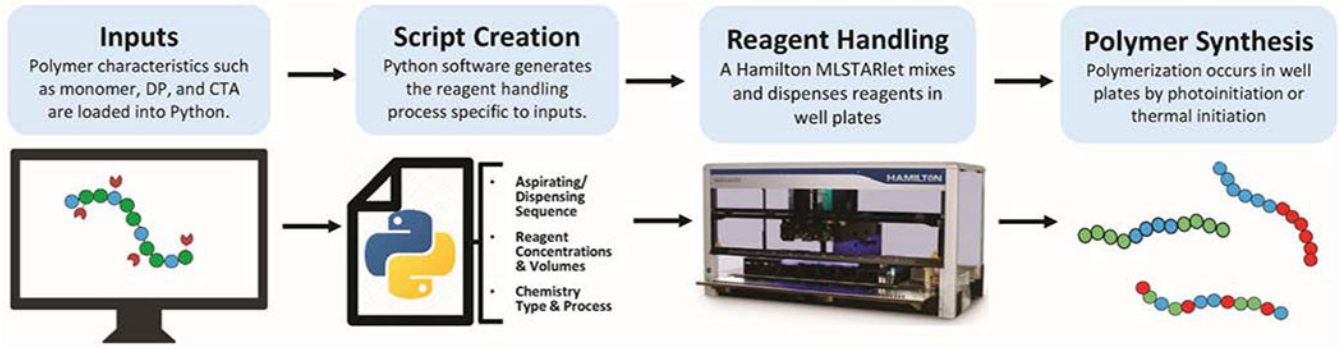


Fig. 3.

Schematic of automated polymer synthesis workflow incorporating liquid handling robotics and open-air Enz-RAFT and PET-RAFT. User inputs such as DP, polymer composition, and CTA type are supplied to a Python script which produces pipetting sequences, concentrations, dispensing volumes, and process information. The Hamilton MLSTARlet liquid handling robot carries out the open-air chemistry directly in 96-well plates. This process is compatible with homopolymers, random heteropolymers, and block copolymers [10]. Reproduced with permission from Wiley-VCH Verlag GmbH & Co. KGaA. License can be found online (https://creativecommons.org/licenses/by/4.0/).

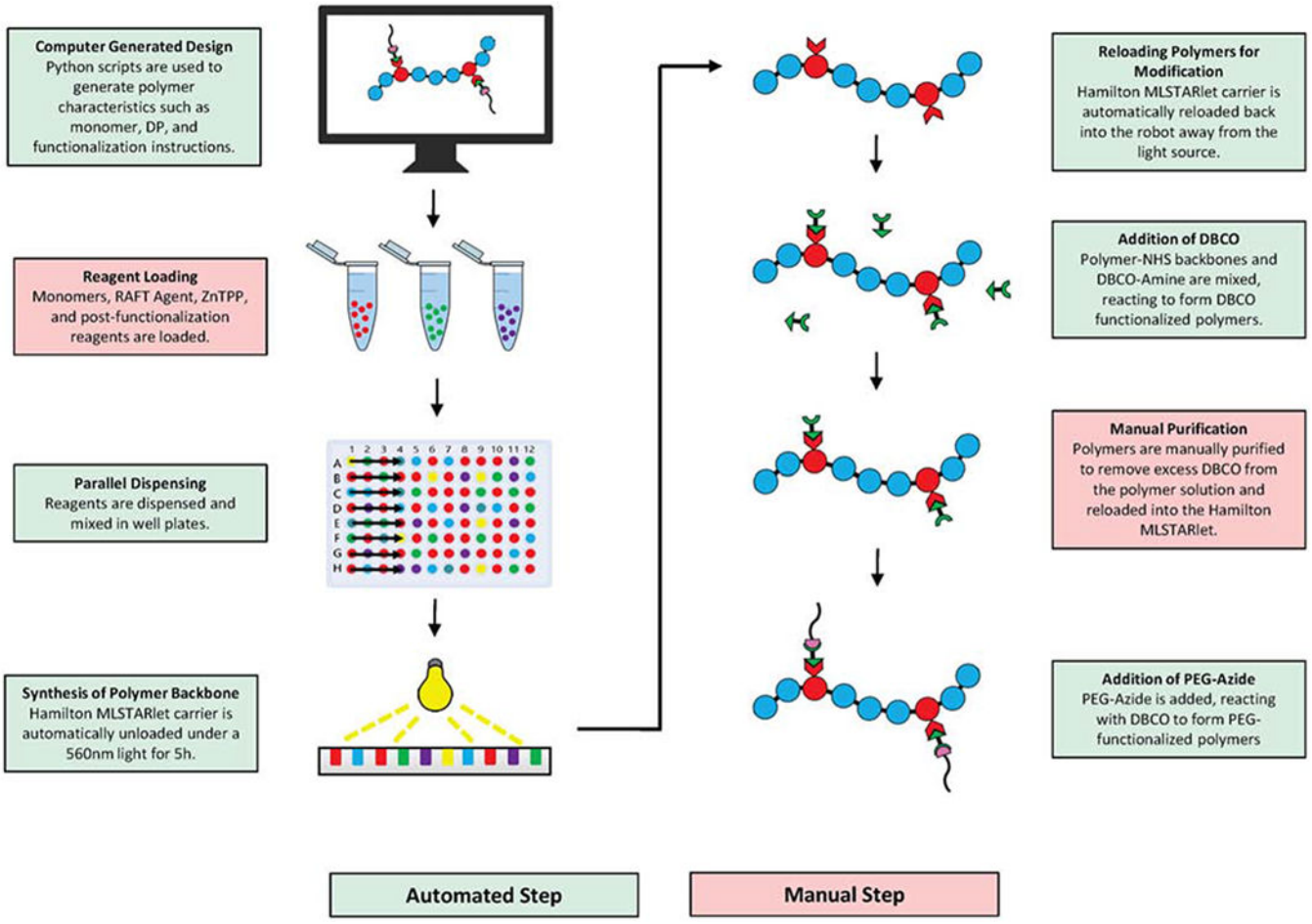
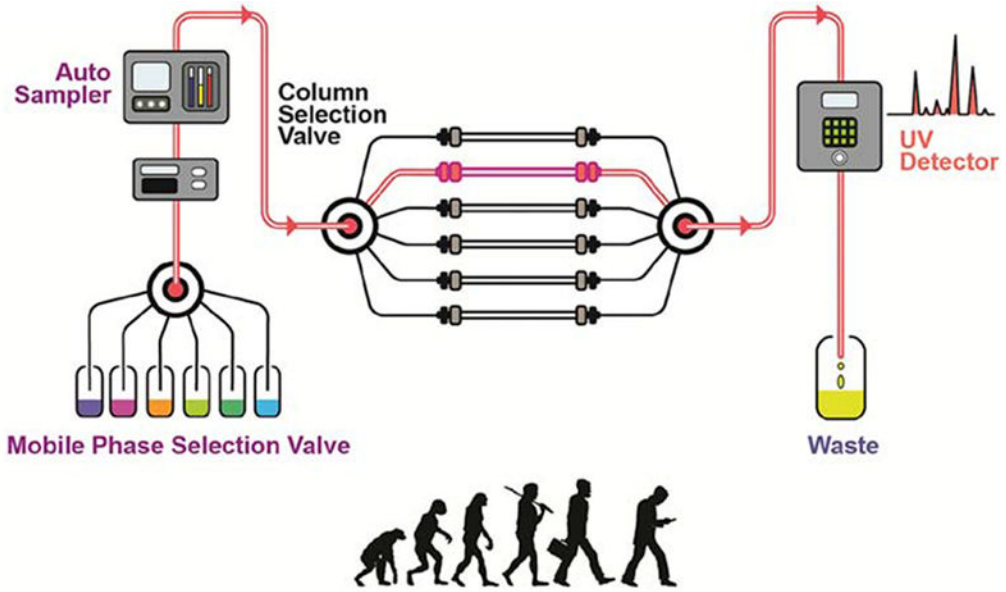


Fig. 4.

Automated synthesis of functionalized polymers. The user first designs the polymer library by specifying DP, composition, and functionalization information. Reagents are loaded by the user and then the liquid handling robot carries out dispensing steps. Post-polymerization modification was validated for strain-promoted azide-alkyne cycloaddition (SPAAC) [10]. Reproduced with permission from Wiley-VCH Verlag GmbH & Co. KGaA. License can be found online (https://creativecommons.org/licenses/by/4.0/).



Conditions	1990s →		2005 →			Current
Column size (mm)	250 x 4.6	150 x 4.6	100 x 4.6	100 x 2.1	100 x 3.0	100 x 2.1
Particle size (μm)	10	5	3.5	<2	2.7*	<2*
Approx. run time (min)	60	40	35	15	20	10
Max system pressure (bar)	200	400	400	1000	600	1000
Available pH range	2-7	2-9	2-11	2-11	2-11	2-11

* Superficially porous particles

Fig. 5.

Evolution of analytical chromatography from the 1990s to the present day. Over time, the limits of column size, particle size, and run times have dramatically decreased. Higher pressure limits and a wider pH range are also possible [132]. Reproduced with permission from Elsevier.

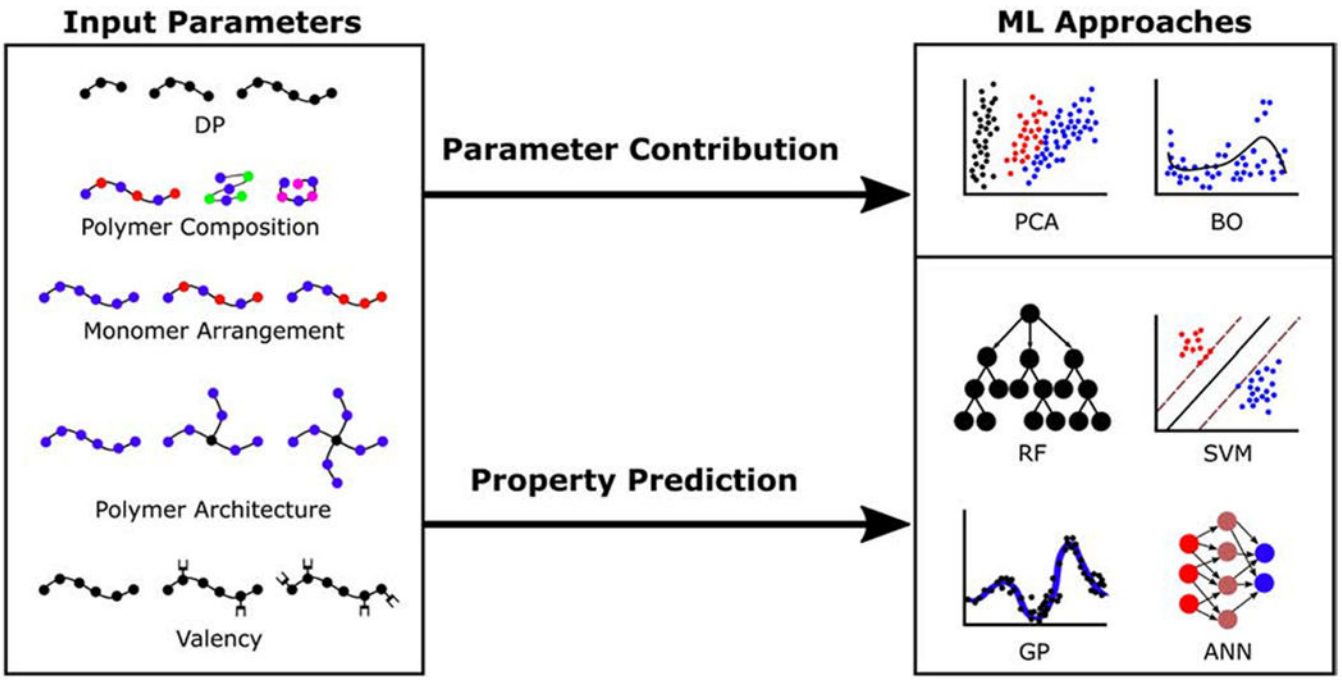


Fig. 6.

ML approaches in the context of polymer chemistry. In polymer chemistry, relevant input parameters that can be controlled via the selected synthetic approach are DP, polymer composition, monomer arrangement, polymer architecture, and valency. PCA and BO aim to determine which parameters most contribute to the variance in data while RF, SVM, GP, and ANN can be utilized in property prediction.

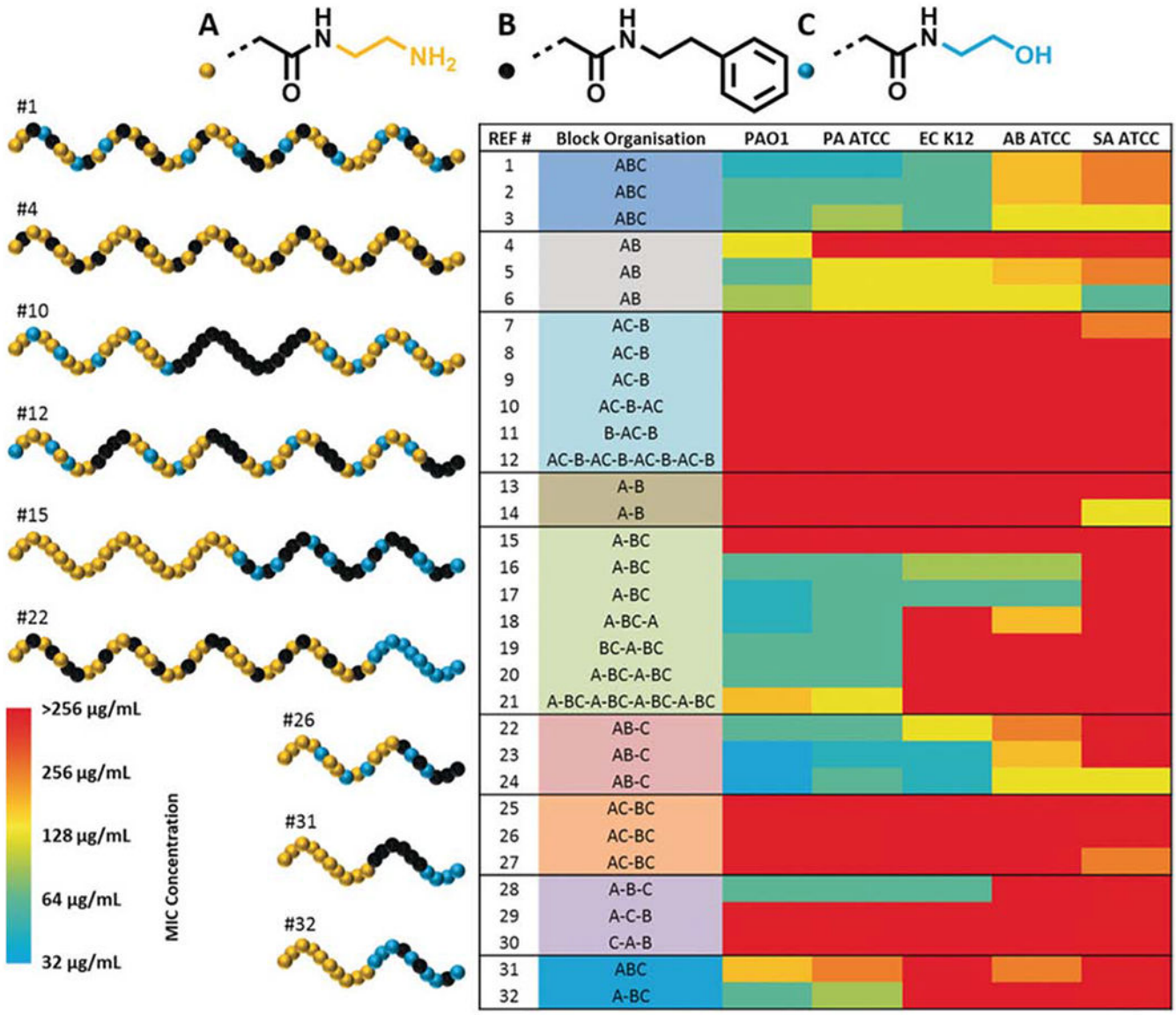


Fig. 7.

Representation block organization of polymers alongside a heat map of MIC for each. This enabled identification of hit polymer candidates that exhibited high bioactivity and warrant closer consideration [161]. Reproduced with permission from Wiley-VCH Verlag GmbH & Co. KGaA.

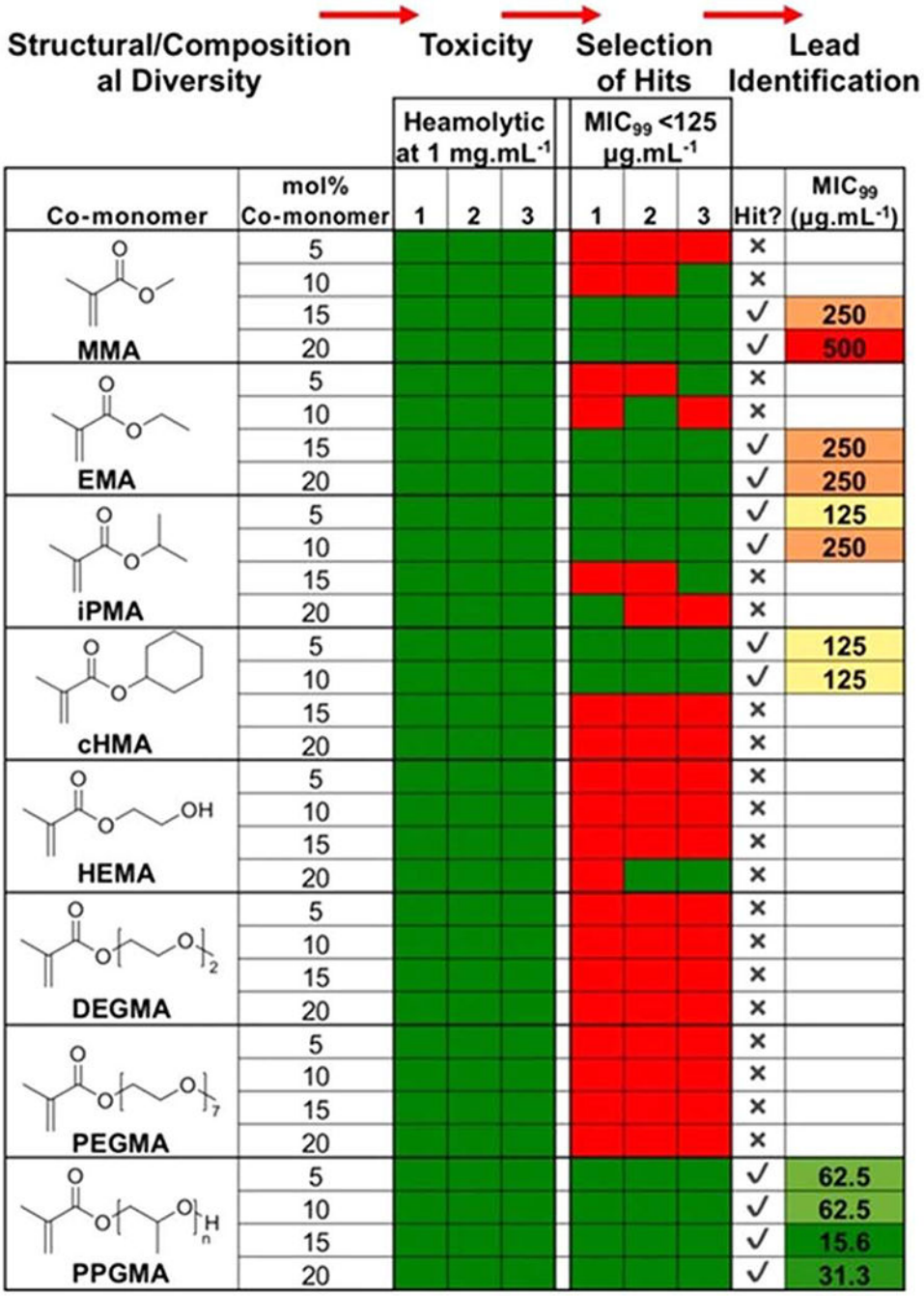


Fig. 8.

Characterizing toxicity and screening antimicrobial polymer candidates after automated synthesis. Along with base monomer PDMAEMA, co-monomers were chosen and synthesized into the polymer backbone at varying mol%. There was shown to be minimal hemolytic activity for all polymers. PPGMA was identified to have the most bioactivity overall as the most hydrophilic monomer [25]. Reproduced with permission from Wiley-VCH Verlag GmbH & Co. KGaA.

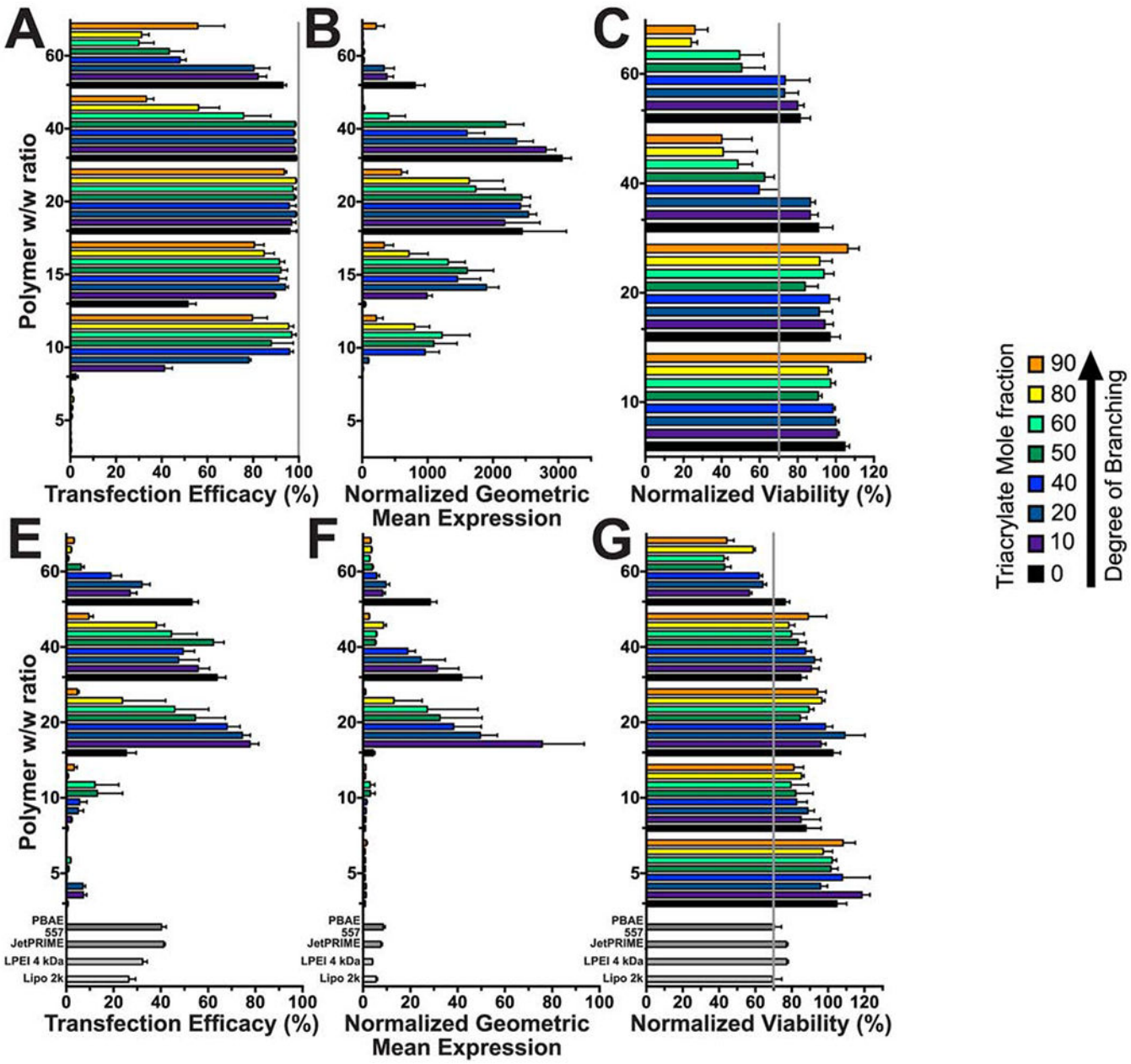


Fig. 9.

The effect of polymer concentration and degree of branching on transfection efficacy, expression, and viability. A rapid combinatorial synthesis approach allowed further study of these conditions prior to additional screening experiments. Reprinted and adapted with permission from the American Chemical Society. Copyright 2019 American Chemical Society [174].

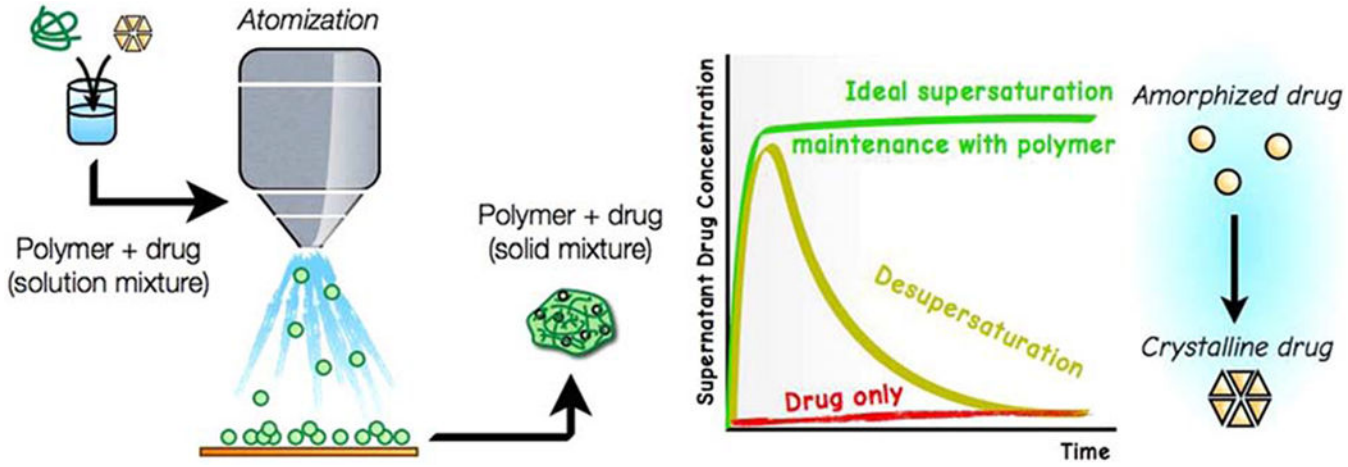


Fig. 10.

Preparation and mechanism of ASD interaction with drug. ASDs shown are prepared via spray drying to form a polymer and drug solid mixture. Polymer-drug interactions, typically through non-covalent interactions, enable API supersaturation whereby precipitation or crystallization of API is prevented over a long period of time. Reprinted with permission from the American Chemical Society. Copyright 2015 American Chemical Society (https://pubs.acs.org/doi/10.1021/acsbiomaterials.5b00234) [176]. Requests for permissions should be directed to ACS.

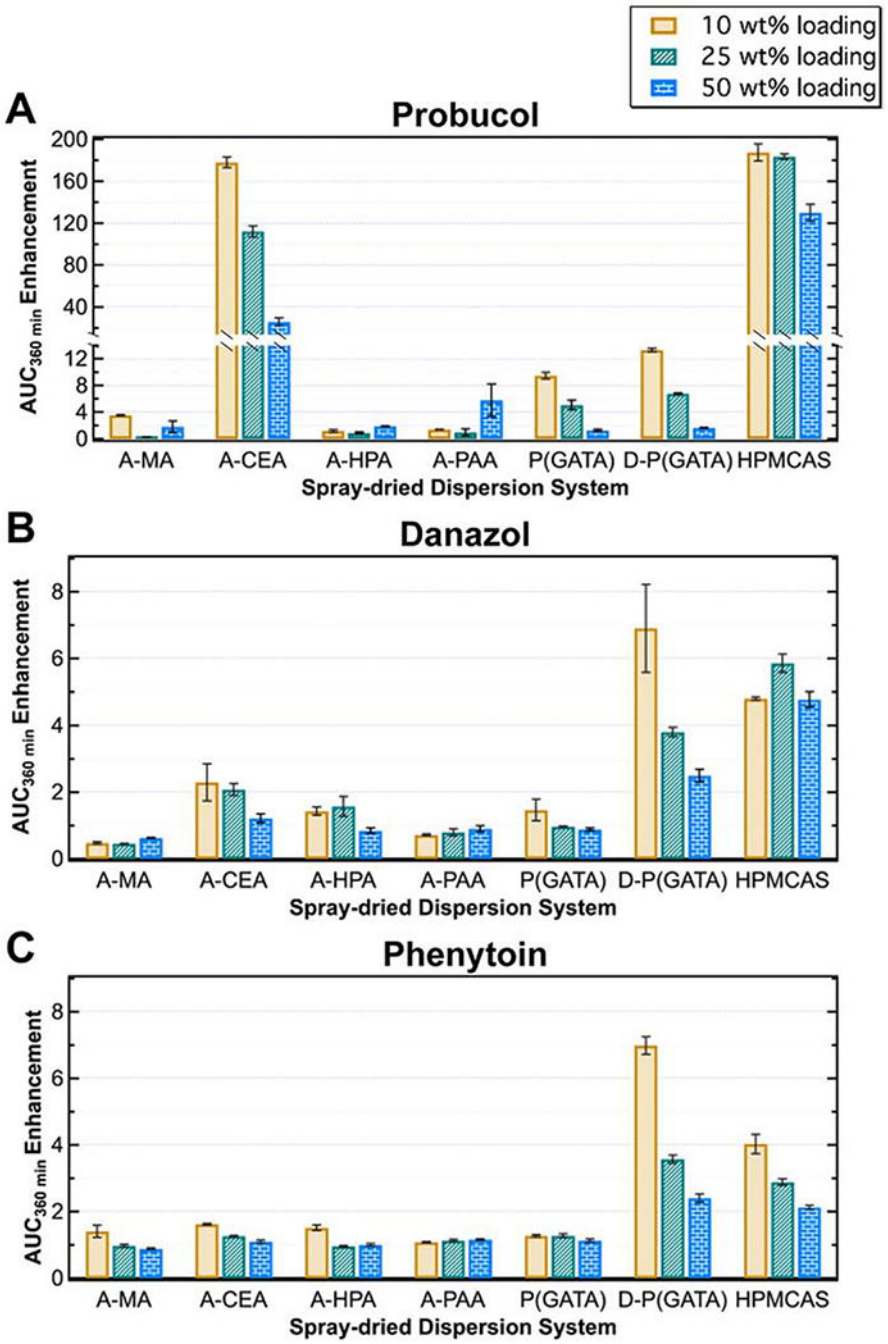


Fig. 11.

Comparison of various modified HPMCAS polymers for supersaturation of probucol, danazol, and phenytoin at different drug wt% (10, 25, and 50 wt%). CEA-modified HPMCAS performed best in dissolving probucol, likely due to hydrogen bonding and hydrophobic interactions. Reprinted with permission from the American Chemical Society. Copyright 2015 American Chemical Society (https://pubs.acs.org/doi/10.1021/acsbiomaterials.5b00234) [176]. Requests for permissions should be directed to ACS.

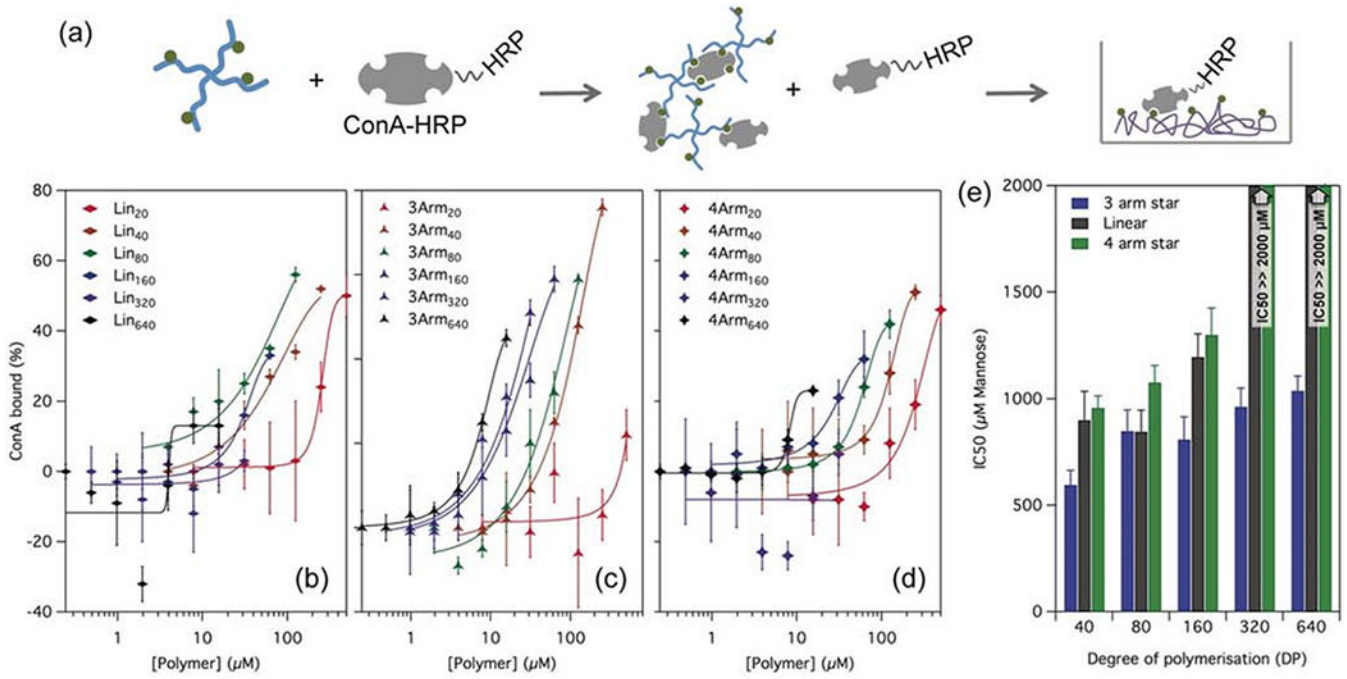


Fig. 12.

Effect of polymer DP and architecture on binding *concanavalin A* (ConA) via a lectin binding assay. The percentage of bound ConA is displayed for various DP linear, 3-arm, and 4-arm polymers. 3-arm polymers performed best, especially at lower DPs, followed by linear and then 4-arm polymers. This illustrates the utility of the combinatorial library approach in determining structure-activity relationships [9]. Reproduced with permission from Wiley-VCH Verlag GmbH & Co. KGaA.

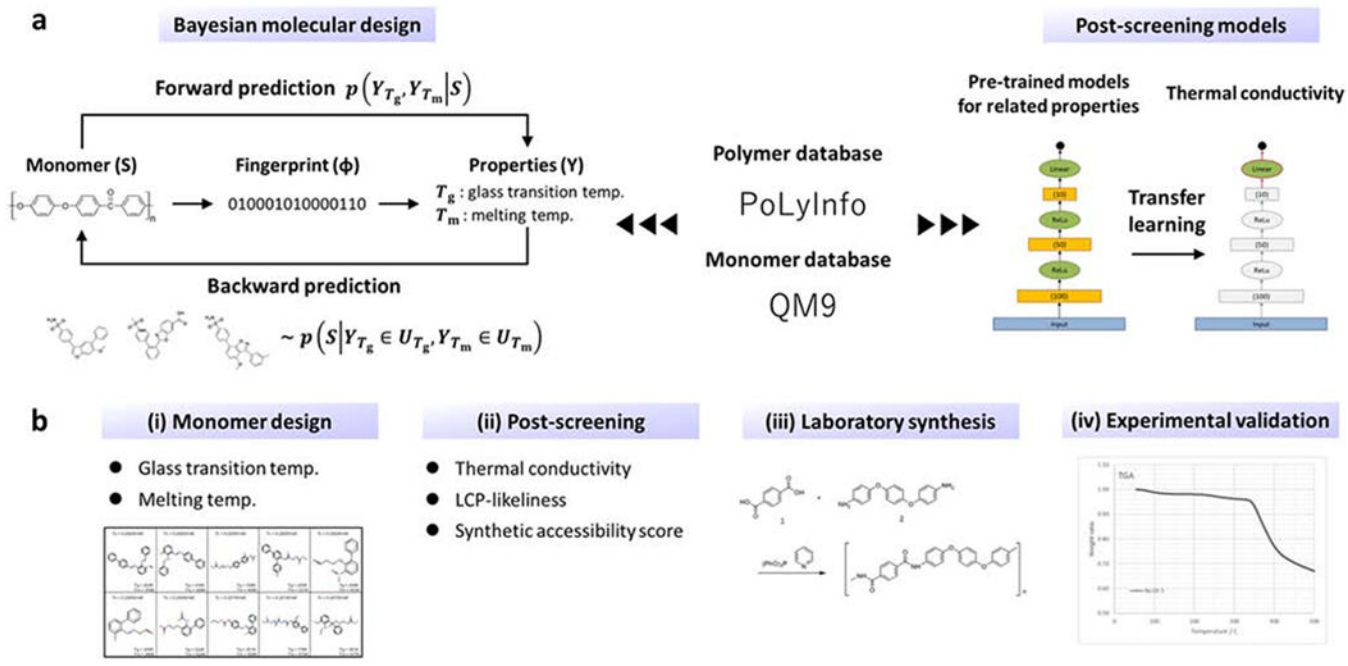


Fig. 13.

ML approach to identify polymers that have high thermal conductivity. Bayesian molecular design was initially conducted to train a model to predict secondary properties of T_g and T_m. Transfer learning was then completed with limited data on thermal conductivity to generate predictions which were verified through the synthesis of three polymers [250]. Reproduced with permission from Springer Nature. License can be found online (https://creativecommons.org/licenses/by/4.0/).

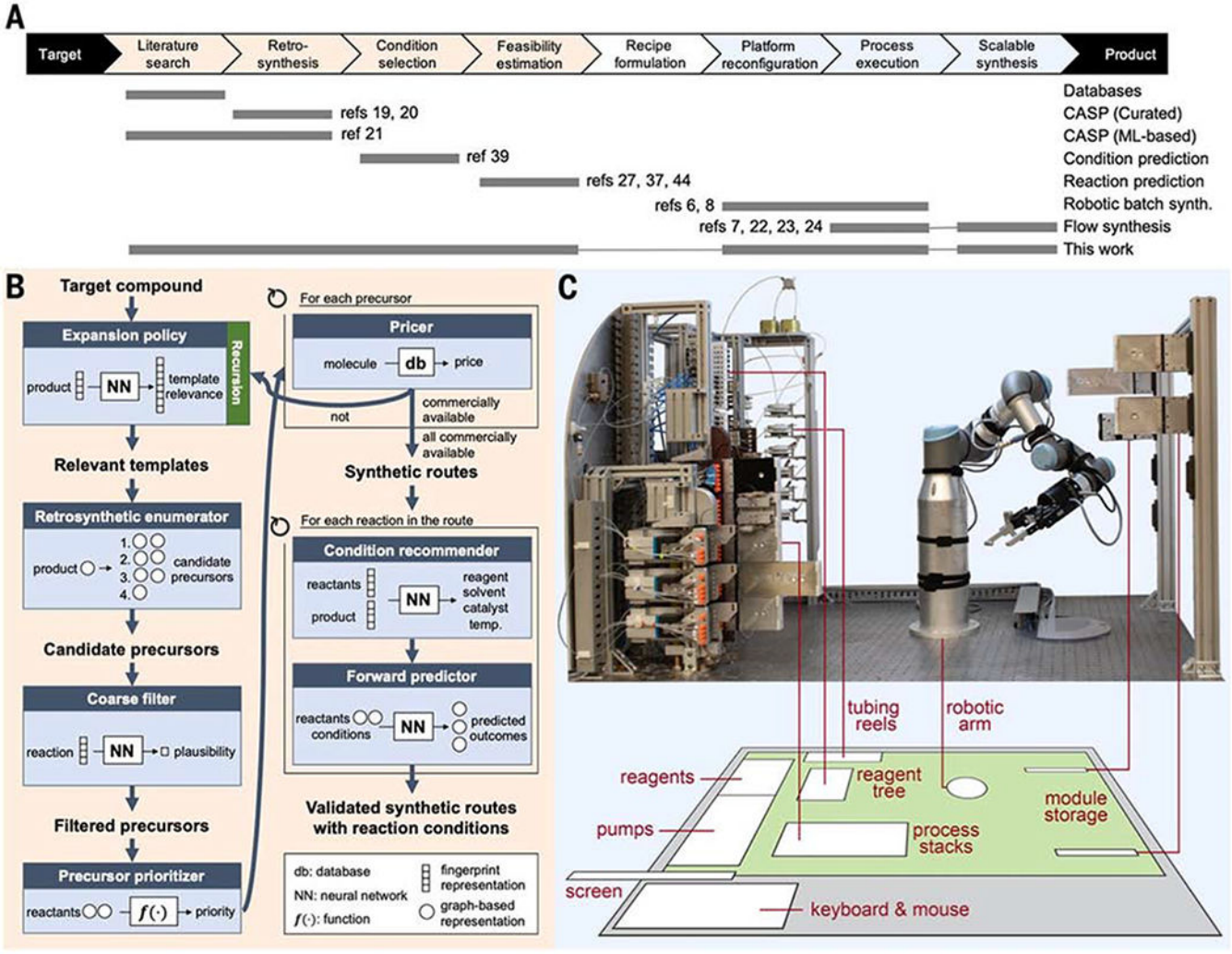


Fig. 14.

Robotic and data-driven design system for CASP. (**A**) Comparison of this work to previously published work (gray bars denote areas in which automation has been achieved). This work has demonstrated automation in every aspect of the organic synthesis process except recipe formulation which requires some user input (e.g. stoichiometry and confirming reaction conditions). (**B**) ML approach that utilizes chemical reaction data found in the Reaxys database. (**C**) Image of the six-axis robotic manipulator along with modular setup of the working area [259]. Reproduced with permission from the American Association for the Advancement of Science.

Table 1.

Comparison of commonly used liquid handling robots

Expertise	Instrument	Features	Compatibility	Integration	Drawbacks	Ref
Beginner	Thermo Scientific Matrix PlateMax 2X3	Compound addition and plating Serial dilutions Modular	96, 384, 864, and 1536-well plates Reagent reservoirs	Barcode reader	Less customizable	[119, 120]
	Andrew Alliance Andrew+	Anthropomorphic control of pipettes Modular Object recognition and vision-guided movement Remote protocol setup and execution Remote protocol design, execution, and monitoring	96-well plates Centrifuge tubes Reagent reservoirs	Handheld electronic pipettes	Less customizable Complex movement	[121]
	Integra VIAFLO 96/384	Plating reagents or cells	96 and 384-well plates Reagent reservoirs	None	Less customizable Semi-automated 2 plate capacity Not compatible with other labware	[30, 122–124]
	Integra ASSIST PLUS	Compound addition Serial dilutions	96 and 384-well plates Reagent reservoirs	None	Less customizable 2 plate capacity Incompatible with other labware	[125]
	Rainin Benchsmart 96	Automated mixing Plating reagents or cells	96-well plates Reagent reservoirs	None	Less customizable Semi-automated	[126]
Intermediate	Beckman Coulter Biomek i7	Modular Simulator Data management Remote monitoring	96 and 384, and 1536-well plates Centrifuge tubes	Barcode reader Grippers UV-vis Centrifuge Flow cytometry High content imaging Plate labelers	Less customizable	[127]
	Chemspeed Accelerator SLT100	4-needle head	Reaction vessels Test tubes	Temperature control	Incompatible with other labware Limited capacity	[114–117, 128]
	Unchained Labs Big Kahuna	Modular Powder dispensing and liquid handling Contains grippers Formulation	96-well plates with multiple substrate Vials	Grippers Heating and stirring Can use plates compatible with polarized light microscopy, PXRD, and Raman spectroscopy	Incompatibility with other instruments Influenced strongly by dispensing head and environment Requires expertise	[95, 129]
	Opentrons OT-2	Modular 2-pipette mount Open Source	96 and 384-well plates Centrifuge tubes	Thermocycler Magnetic Module Temperature Module	Less customizable Not compatible with external characterization instruments	[130–132]
Advanced	Chemspeed SWING	Modular Programmable Rapid dispensing Powder dispensing and liquid handling Dispensing range from mg-g scale Formulation and library synthesis	96-well plates Vials Reaction vessels	Excel data storage of conditions (mixing speed, temperature, time)	Error-prone Require outside intervention	[133]

Expertise	Instrument	Features	Compatibility	Integration	Drawbacks	Ref
	Tecan Freedom EVO	Modular Programmable Various size models Simulation	96 and 384-well plates Centrifuge tubes Reagent bottles	Barcode reader 7 types of robotic arms UV-vis plate reader	Technical expertise needed to program	[15]
	Hamilton Microlab	Modular Programmable Simulation	96 and 384-well plates Centrifuge tubes Test tubes	Barcode reader Grippers and robotic arm UV-vis Automated plate sealer Incubator	Technical expertise needed to program Time-consuming liquid class setup	[10]