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Controlled release from recombinant polymers

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ABSTRACT

Recombinant polymers provide a high degree of molecular definition for correlating structure with function in controlled release. The wide array of amino acids available as building blocks for these materials lend many advantages including biorecognition, biodegradability, potential biocompatibility, and control over mechanical properties among other attributes. Genetic engineering and DNA manipulation techniques enable the optimization of structure for precise control over spatial and temporal release. Unlike the majority of chemical synthetic strategies used, recombinant DNA technology has allowed for the production of monodisperse polymers with specifically defined sequences. Several classes of recombinant polymers have been used for controlled drug delivery. These include, but are not limited to, elastin-like, silk-like, and silk–elastin-like proteins, as well as emerging cationic polymers for gene delivery. In this article, progress and prospects of recombinant polymers used in controlled release will be reviewed.

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1. Recombinant polymers

Natural proteins have a predesigned function eliciting a specific cellular response. This automated behavior is resultant of their primary amino acid sequence that dictates folding patterns and architecture, which in turn commands function [1]. Understanding the central dogma of molecular biology has opened avenues in biomaterial design, particularly engineering recombinant protein polymers for new applications in biological systems. These recombinant polymers are synthesized by harnessing the protein synthesis machinery of cells through genetic engineering and DNA manipulation [2–7]. The sequences of recombinant polymers are often borrowed from naturally occurring proteins grounded on function. DNA sequences of diverse species may be combined or synthetic sequences using non-canonical amino acids like p-fluorophenylalanine or selenomethionine may be introduced, creating novel functions demanded by the chosen application [8]. (See Table 1.)

The early 1970s encompassed pivoting work by biochemists including Lobban, Kaiser, Berg, and Khorana who developed biochemical methods for inserting new genetic material in pre-existing DNA of a bacteriophage, paving the way for chemical syntheses of genes and recombinant DNA technology [9–12]. One of the earliest works describing synthesis of a recombinant polymer in a biological system was by Doel and coworkers in 1980 where a defined DNA sequence was made via phosphotriester methodology and subsequently cloned into *Escherichia coli* using plasmid vectors with controllable promoters [4]. *E. coli* expression yielded a simple polymer of phenylalanine and aspartic acid that is enzymatically degradable [4]. Synthetic methods of more complicated polymers composed of repetitive co-polypeptides began to be established in the late 1980s and early 1990s including work by Fournier, Tirrell, and Cappello [2,5,8,13–15]. Both chemical synthesis and genetic strategies were explored. McGrath et al. described both techniques to create co-polypeptides [-(GlyAla)$_3$-GlyProGlu-]$_n$, the first a purely chemical synthesis via classical solution phase methods, yielding a polydisperse product of average molecular weights less than 100,000 Da, followed by recombinant DNA methods where chemically synthesized oligomers were self-ligated resulting in multimers subsequently incorporated into expression plasmids with appropriate translation signals. *E. coli* expression of the plasmids yielded monodisperse product [5]. This work is a powerful example indicating key differences in polymer synthesis strategy.

Although, synthetic polymers have been designed in parallel with recombinant polymers for similar applications, there are several advantages to recombinant polymers over their chemically synthesized counterparts. First, the level of control by nature's cellular machinery to make macromolecules remains unsurpassed [1]. When recombinant polymers are made in a biological system, such as bacteria, the product is virtually monodisperse in both sequence and size. Each polymer strand is an exact copy generated from a DNA template, which was previously designed and transferred into the production cell line [16]. This monodispersity can be important in drug delivery applications to enable generation of distinct release profiles and determine structure–function relationships that may not be possible with a statistically defined polymer system. Chemically synthesized macromolecules cannot match this precision especially in more complicated and longer chain

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Table 1
Common amino acid sequences and main structural components of recombinant polymers discussed in this review. ELP: Elastin-like Polypeptides, SLP: Silk-like Proteins, SELP: Silk–Elastinlike Protein Polymers.

Recombinant polymer	Consensus sequence	Representative structural motif	Ref
ELP	$(VPGXG)_n$ (X is any amino acid other than proline)	Temperature-induced phase separation behavior, resulting in aggregation and formation of an insoluble coacervate. Cysteine can be added for conjugation, or lysine residues for crosslinking.	[21,22]
Di-block	$(GVGVP)_m$ $(GXGVP)_n$ (X is any amino acid other than proline)	Self-assemble into spherical micelles for given lengths and ratios of hydrophobic and hydrophilic blocks.	[21,22]
Tri- block	$[(VPAVG)$-$(IPAVG)U(VPGXG)_n][(VPAVG)$-$(IPAVG)_4]_p$ (Middle hydrophilic sequence less conserved)	Hydrophilic block capped on both ends by hydrophobic blocks will lead to spherical or cylindrical worm-like micelles	[21,23,63]
SLP			
Spicier silk	$(G)_m(A)$, GPGXX (X is most likely glutamine, but can vary)	Repetitive alanine and glycine create high tensile strength crystalline structures. The pentapeptide contributes to formation of 3-spirals.	[76]
Silk worm	$(GAGAGS)_m$, $(GAGAGY)_n$, $(GAGAGA)_p$ or $(GAGYGA)_q$	The hexapeptides form crystalline (3-sheet structures due to the dominance of hydrophobic domains	[76]
SELP	$[(GVGVP)_mGKGVP(GVGVP)_n(GAGAGS)_p]_q$	Physical networks form as silk-like units collapse into (3-sheets, and elastin-like units collapse into helical structures contributing to porosity	[33]

length polymers, which often generate statistical distributions of polymer lengths. Fig. 1 depicts general recombinant protein engineering methodology, which begins with design of the amino acid sequence for the desired product. The DNA sequence is synthesized using solid phase techniques. Often, the final product consists of repeats of a single sequence; therefore a small oligomer is synthesized followed by a multimerization process and enzymatic ligation into a DNA plasmid vector. Multimerization can be considered a polycondensation event where designed sticky ends of the oligomers bind, creating random length multimers. Once the multimers are ligated into the vector, a host cell, often a bacterium like *E. coli*, is transformed and grown as individual colonies for plasmid screening. The screening allows determination of multimer size and consequently isolation. Isolated plasmid is re-transformed into a host cell and large scale fermentation and purification of product ensues [1,8]. Expression vectors are designed to have a switch, such that the protein is only expressed at high bacterial density. Switches may be chemically or temperature induced. Premature protein synthesis will hinder bacterial growth and product yield will be low [1].

Second, recombinant polymers are often biodegradable as they are constructed of simple amino acid residues and degrade into small peptides or single amino acids [17]. Third, recombinant polymers can be systematically altered in order to generate libraries of potential candidates or investigate the exact role of individual components of the polymer system on properties important for controlled release such as mechanical integrity, bioactive agent release, biorecognition, degradation and elimination. The Urry group systematically approached the synthesis of peptide-based polymers to understand how different biophysical properties change with methodical change in polymer sequence [18]. They began by constructing a basic gene unit encoding $(GVGVP)_{10}$ and building concatemer genes with varying repeats of the monomer unit, creating macromolecules greater than 100,000 Da. This work, along with other work using sequential poly peptides synthesized

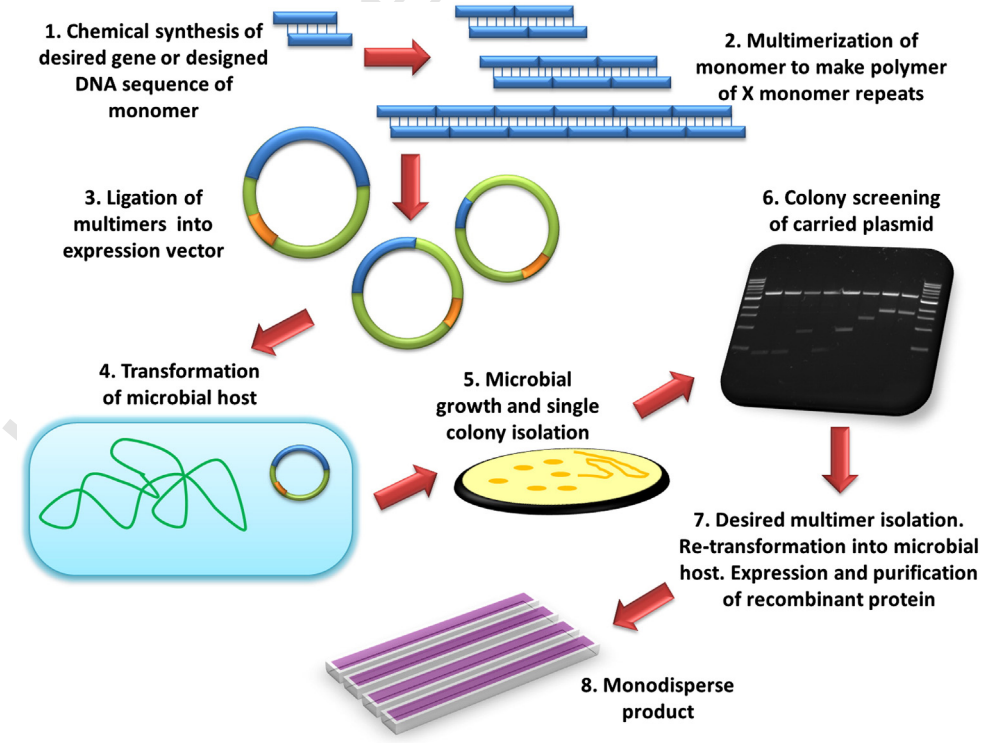

Fig. 1. Generalized schematic of recombinant polymer synthesis.

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