Digging into the Sequential Space of Thiolactone Precision Polymers: A Combinatorial Strategy to Identify Functional Domains

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**Abstract:** Functional sequences of precision polymers based on thiolactone/Michael chemistry are identified from a large one-bead one-compound library. Single bead readout by MALDI-TOF MS/MS identifies sequences that host *m-*THPC as second generation photo-sensitizer drug. The corresponding Tla/Michael-PEG conjugates render *m-*THPC available in solution and drug payload as well as drug release kinetics can be fine-tuned by the precision segment.

Synthetic macromolecules with discrete monomer sequences promise to resemble information rich biomacromolecules such as proteins, nucleotides or oligosaccharides.[1] A{Lutz, 2013 #18}rtificial precision polymers offer opportunities to advance materials science by programming recognition capabilities.[2] A glance on the potentials of precision polymers can be found in the class of biohybrid polymers, which contain discrete biosegments.[3] These hybrid macromolecules enable the realization of exciting functions like peptide/DNA guided self-assembly, material specific coatings or anchors, as well as enzyme activable glues and selective interface stabilizers/compatibilizers.[4]

Significant attention was devoted to establish means to prepare monodisperse macromolecules with defined monomer sequences.[5] Several solution-phase strategies were explored, including radical chain growth of either spontaneous sequence forming or templated monomer pairs, but also radical polymerization under single monomer insertion conditions, and ring opening metathesis of cyclic macromonomers.[6] Alternatively, routes expanding solid-phase synthesis (SPS) strategy can successfully yield monodisperse oligomers from synthetic monomer alphabets. This resulted in diverse precision polymer platforms from a broad range in chemistries.[7] Among those, Du Prez *et al.* introduced an iterative submonomer synthesis route that includes thiolactone isocyanate (Tla-NCO) coupling to hydroxyl-functional supports. The synthesis cycle is completed by Tla ring opening with 2-aminoethanol, which deprotects the thiol that subsequently adds to acrylates via Michael addition and generates a hydroxyl group (Fig. 1). Repetition of the reaction cycles with a variety of acrylates lead to sequence-defined Tla/Michael-oligomers.[8] The strategy was automatized and adapted to poly(ethylene glycol) (PEG) preloaded supports to access PEG*-block-*Tla/Michael-oligomers.[9]

While the development of synthesis strategies for precision polymers was until recently considered the main challenge, the quest for sequence-based functions to exploit these sophisticated polymers has to be put into focus. A few examples such as data storage, anti-microbial activity and anti-counterfeiting were described,[10] but a wide range of applications is yet to come.

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**Figure 1.** Combinatorial selection of functional Tla/Michael-oligomer sequences with specific solubilizer properties. On-support synthesis of Tla/Michael-oligomers (i) leading to a combinatorial one-bead/one-compound library (ii) that is screened for drug binders (iii). Single bead sequence readout of positive hits by MS/MS fragmentation (iv) provide sequences for drug solubilization tests (v).

Recently, PEG-peptide conjugates proved high potential as precision formulation additives to render poorly soluble drugs water soluble and improve bioavailability for drug structure testing.[11] The peptide sequences were selected from large peptide libraries, providing sequence- or even drug-structure specific interactions to host drugs in transport systems.[12] The generic concept was shown for Kinase IspE inhibitors for malaria therapy, photosensitizers for photodynamic cancer therapy, and Tau-protein aggregation inhibitors/disaggregators for anti-Alzheimer therapy.[13] However, peptides are composed out of natural amino acids, which limits the chemical space available. Synthetic precision polymers, instead, are offering an almost unlimited set of building blocks, having often a higher functional density per repeat unit and showing tuneability of both repeat-unit spacings as well as conformational flexibility in backbone and side chains. Additionally, peptides potentially exhibit the inherent risk of immunogenicity that could limit (bio)applicabilities. Synthetic polymers hold the promise of being less immunogenic,[14] turning precision polymers into a platform that combines the precision of a sequence with the compatibility of non-biorelated polymers.

Here, we present combinatorial means to select sequences of Tla/Michael-oligomers having specific functions. Therefore, a one-bead one-compound (OBOC) precision polymer library was prepared by split-and-mix protocols and the single-bead sequence readout by fragmentation mass spectrometry was established to identify functional precision polymer segments for rendering 5,10,15,20-tetra-kis(3-hydroxyphenyl)chlorin (*m-*THPC), a promising second generation photosensitizer, water soluble (Fig. 1).

Prior to spanning the sequential space of Tla/Michael-oligomers in an OBOC library, the sequencing was studied for a Tla/Michael-pentamer model that was synthesized on a Gly preloaded resin (**SEQ0**). Ultra performance liquid chromatography (UPLC) proved the monodispersity of **SEQ0**. According to the order of acrylates used during the synthesis, **SEQ0** was supposed to present Gly and methyl, isobutyl, 2-phenoxy ethyl, ethyl and ethyl side chains, in that discrete order (Fig. 2 and S.I.).

**Figure 2.** Chemical sequence structure (a) and sequence analysis (b) of **SEQ0**. UPLC-ESI MS chromatogram proved clean synthesis (b, inset with target ion and # TFA adduct). MALDI-TOF MS/MS analysis shows systematic fragmentation pattern enabling sequence reconstruction.

The fragmentation of **SEQ0** shows a discrete ladder-type pattern in MALDI-TOF tandem mass spectrometry (MALDI-TOF MS/MS). The parent ion is almost completely consumed and the thioether-linked side-chains of the structure stays intact. Under the given collision induced dissociation fragmentation conditions, primarily single point fragments at the urethane linkage are found, leading to prominent [b] and [y] fragments. This keeps the sequence information accessible, making the Tla/Michael-oligomer class highly suitable for sequence assignment (Fig. 2).

After establishing sequence readout, a combinatorial one-bead/one-compound library of Tla/Michael-oligomers was synthesized by combining previously described synthesis conditions[9] with split-and-mix protocols (cf. S.I.).[15] The Chemmatrix® resin was the support of choice, which proved suitability for on bead screening in aqueous media. The one-bead/one-component Tla/Michael-oligomer library was constructed aiming at Tla/Michael-pentamers by using six different acrylates (benzyl-, isobutyl-, ethyl-, methyl-, 2-methoxyethyl- and 2-(2-ethoxyethoxy)ethyl-acrylates, S.I. Fig. S4) The set covers a range of polarities and offers suitable interaction capabilities with the aromatic and hydrophobic drug structure of *m*-THPC that was used as model drug. Taking the six acrylates and 5mer domain of the Tla/Michael-oligomers into account the library spans 7776 sequence variations with at least 30 replicas. Single bead sequence readouts were successfully tested at original Chemmatrix® library beads (Fig. 3). A transfer of the fragmentation behavior as found in the fragmentation study of **SEQ0** was feasible. To prepare for high throughput screening, the observed modes of fragmentation were implemented into a newly programmed software code (cf. S.I.).[16] The parent mass signal [M+Na]+ could be identified as the most intensive peak and the fragment ions enabled assignment of the test sequence (Gly-[Tla/Michael-pentamer] with 2-methoxyethyl-, 2-(2-ethoxyethoxy)ethyl-, benzyl-, isobutyl-, methyl-, methyl-acrylate side chains from urea- to hydroxyl-terminus.

To identify functional sequences, a screening of the sequence space was executed, selecting drug binders that should render the *m*-THPC water soluble. For that purpose, the OBOC-library of Tla/Michael-oligomers was incubated with *m*-THPC. Fluorescence microscopy enabled to follow the partitioning of *m*-THPC in the library. 15% of the beads show a significant enrichment of *m*-THPC, suggesting that the screening process occurs with sufficient selectivity (Fig. 3 and S.I. Fig. S1). Those beads, exhibiting fluorescence were isolated by handpicking and sequence readout by MALDI-TOF MS/MS revealed the sequences of the Tla/Michael-oligomer domains (S.I. Tab. S1). A set of negative controls have been picked in addition to the positive hits to analyze Tla/Michael-oligomer sequences that are *m-*THPC non-binders (S.I. Tab. S2).

**Figure 3.** Single bead analysis of Tla/Michael-oligomers as selected from library screening. MALDI-TOF MS proved clean build-up of the oligomers (a) and MALDI-TOF MS/MS enables sequence read out from single beads (b) to identify a set of *m-*THPC binding sequences (c, SEQ1-3) and a non-binder control (c, SEQ4) that are subject to further studies as SEQ-PEG conjugates.

The automated analysis of MS/MS-fragmentation data of 65 beads (50 binders (+) and 15 non-binders (-)) revealed 35 unique positive and 10 negative Tla/Michael-oligomer sequences with a success rate of ~70% (S.I. Tab. S1).

Global sequence evaluation of *m*-THPC binders identifies high propensities for benzyl and isobutyl side chain residues to occur, while hydrophilic residues were strongly depleted (S.I. Fig. S6). The efficiency of the screening process to identify drug binders with residues relevant for drug interactions, was evident by evaluating the non-binder sequences, where benzyl moieties are fully absence and isobutyl groups are largely depleted in comparison to the binder sequences (S.I. Table S2). It therefore appears that hydrophobic and aromatic contacts were important for *m-*THPC accommodation. Motif analysis revealed that the benzyl-residues occur predominantly as dyad, which is in analogy to recently selected peptide-based *m*-THPC binders showing Phe-Phe dyads to be preferred.[11]

From the set of Tla/Michael-oligomers, three related sequences have been chosen with the rational of a systematic sequence variation (Fig. 3, SEQ1-3). The sequences preserve a central benzyl-dyad and have polar residues at position 5 (methyl or 3-methyl-3-oxapropyl), while positions 1-2 show alternations in hydrophobicity. Moreover, **SEQ4** was chosen from the set of non-binders as one of the most hydrophobic control sequences. All sequences were synthesized as Tla/Michael*-block-*PEG conjugates by SPPS on PAP resins (**SEQ1-4-PEG,** S.I.).[9]

Drug solubilization experiments, using forced loading procedures[11] have shown that all Tla/Michael-oligomer-PEGs that contain binding sequences can solubilize *m*-THPC (Fig. 4A). Only minor differences in payload were found for the solubilizers **SEQ1-PEG** and **SEQ2-PEG**, both reaching capacities of about 1:2 mmol drug per mmol carrier. The capacity is superior to the best performing peptide-PEG conjugate that has reached 1:3.1 (mmol drug per mmolcarrier).[11] However, when the benzyl side chain at position 1 was replaced by a methyl group (**SEQ2-PEG** *vs.* **SEQ3-PEG**) the capacity evidenced a 60% decrease to 1:5 (molar ratio drug : carrier). The sensitivity of the solubilizer payload concerning single residue exchange seems to be notable and the found effect is beyond the expectable one for a decrease in the volume fraction of the hydrophobic segment. Moreover, the control **SEQ4-PEG** that presents a non-binding sequence has significantly lower capacities of 1:17. Apparently, the capacity to host *m-*THPC originates not exclusively from the large volume fraction of the Tla/Michael-oligomer backbone but is sensitive to side chain functionalities and single point mutations.

To elucidate the sequence effects on solubilizer capacity in more detail, **SEQ1-PEG** and **SEQ2-PEG** analogues were synthesized that were composed of the same residues but exhibit a scrambled residue order (**SEQ1\*-PEG** and **SEQ2\*-PEG**, cf. S.I. ). The residue scrambling slightly reduced the payload from about 1:2.0 to 1:2.8 and 1:3.2 (mmol drug per mmol carrier), respectively. The scrambling affects the payload capacities less profoundly compared to effects observed with peptide conjugates.[11] This might be rationalized by a reduced conformational flexibility of peptides versus Tla/Michael-oligomers. Apparently, the latter offers -despite the not ideal sequence- still adaptability to optimize drug-solubilizer contacts. However, the selected sequences **SEQ1** and **SEQ2** show by far the highest payload capacities and regardless of the higher backbone flexibility confirm a notable sequence dependency.

To gain insights into the type of drug solubilization, solutions of the *m*-THPC**/SEQ-PEG** complexes were analyzed by dynamic light scattering (DLS, S.I. Fig. S14). DLS measurements of all conjugates show in the absence of *m-*THPC broad, multimodal size distributions and indicate dynamic ill-defined assemblies, which could be expected considering the hydrophobic nature of the Tla/Michael-pentamer sequences and their capabilities to form hydrogen bond networks (data not shown). In contrast to this, all drug/solubilizer complexes show well-defined assemblies with hydrodynamic radii of Rh = 60-70 nm. The only exception is the control *m-*THPC/**SEQ4-PEG** complexes with Rh = 35 nm. Thus, the aggregate sizes remain below Rh = 100 nm, which make the complexes suitable for biomedical applications. Difference in hydrophilic/hydrophobic balance can affect the aggregation behavior, which might influence drug loading capacities of conjugates with binder and non-binder segments. However, it should be emphasized, that during the selection process of binders and non-binders, the peptides are tethered to a matrix scaffold and differences in drug enrichment at certain beads is primarily due to preferential drug/peptide interactions and different aggregation behavior can be at this stage disregarded.

Besides drug hosting, the ability to release *m-*THPC from drug/solubilizer complexes in biological media is an important aspect in the design of solubilizers for photosensitizers. Fluorescence spectroscopy was used to follow drug release kinetics in aqueous solutions of serum albumin as blood plasma protein (Fig. 4). None of the *m-*THPC/**SEQ-PEG** complexes show fluorescence in the absence of albumin, indicating that *m-*THPC is transported in the core of aggregates in a silent state.[11] The fluorescence of *m-*THPC was, however, regained after addition of albumin to the drug/solubilizer complexes. In analogy to peptide solubilizers, the transition from self-quenched densely packed to molecularly separated *m-*THPC, proceeds by trans-solubilization from solubilizer to the albumin proteins.

**Figure 4**. Properties of SEQ-PEGs with respect to drug hosting capacities (a) and drug release kinetics (b) (Conditions: λex = 417 nm, λem = 653 nm, [BSA] = 100 μM, [m-THPC] = 0.1 μM).

Noticeably, all SEQ-PEG systems act as solubilizers and provide the photosensitizer in a well available format, ready to be transferred to blood plasma protein models. While this is not desired for many drug delivery applications, photosensitizers for photodynamic cancer therapy can in this way exploit the natural transporter proteins for systemic distribution and ensure rapid clearance to avoid undesired long-term photosensitivity.

*m*-THPC/SEQ-PEG complexes with selected binder sequences (**SEQ1-3)** show an overall *m*-THPC release of about 40%, which agrees well with the release behavior from peptide-PEG solubilizers, showing 40-60% overall release.[13b] At this point it seems to be noteworthy that the screening selects high capacity binders and to implement additionally the search for fast releaser sequences or quantitative releasers, the screening procedure had to be performed differently.[17] Apparently, the release kinetics form *m*-THPC/SEQ-PEG complexes, which exhibit binder sequences, depend on the sequence polarity, as faster initial release rates are observed by sequences having higher hydrophilicity (S.I. Tab. S3). It could be speculated, that the polar side chain functionalities contribute to drug transfer at the colloidal interface as found previously for peptide-based solubilizers.[13b] It is evident that from *m-*THPC/**SEQ3-PEG** complexes 35% of the drug was activated within 1.0 h, which corresponds to 85% of the releasable drug. Similar release from *m-*THPC/**SEQ1-PEG** or *m-*THPC/**SEQ2-PEG** complexes occurs within ~2.0 h, which is slower but still suitable for therapy applications (for comparison of initial release rates cf. S.I. Tab. S3). Besides the general polarity, also sequence effects are evident. For instance, the solubilizers **SEQ1\*-PEG** and **SEQ2\*-PEG** with scrambled sequences show reduced payload capacities but significantly higher efficacy of drug release, reaching close to 50% and 70% drug release, respectively (Fig. 4). From *m-*THPC/**SEQ2\*-PEG** complexes about 65% drug was activated within 2 h and afterwards only 5% more were released slowly, which seems to be highly beneficial for photodynamic cancer therapy. The sequence evaluation between scrambled and non-scrambled solubilizers revealed the absence of benzyl dyads. Apparently this motif contributes to drug hosting but retards rapid release. At the other extreme, the release from *m*-THPC/**SEQ4-PEG** complex having the non-binder sequence proceeds the slowest, form the set of solubilizers. Considering the small payload capacity and the 17-times excess of those solubilizers per drug a diffusion limitation might be an obvious reason for a slow release kinetics.

In conclusion, Tla/Michael-oligomers tailored for interaction with *m-*THPC were selected by combinatorial means from a large single-bead/single-compound precision oligomer library. MALDI-TOF MS/MS analysis enabled single bead sequence readout. PEGylation of drug binding sequences provides Tla/Michael-oligomer*-block-*PEG conjugates of which the interaction capabilities with *m-*THPC were studied. A significant sequence dependency is obvious for both drug payload capacities and drug release kinetics, offering the possibility to fine-tune drug transporter properties according to the therapeutic needs.

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**Keywords:** combinatorial chemistry • sequence-defined oligomer • sequencing • solid phase synthesis

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| COMMUNICATION | | |
| Monomer-sequence defined oligomers from thiolactone/Michael-type chemistry, which specifically interact with a photosensitizer drug are selected by combinatorial means from large single beads-single compound libraries by mass spectrometry single bead sequence read out. The corresponding PEG conjugates render the photosensitizer water soluble. Drug payload and drug release experiments exhibit a strong dependence on the sequence of the oligomeric segment. |  | Sensu Celasun, Dario Remmler, Timm Schwaar, Michael G. Weller, Filip Du Prez, Hans G. Börner\*  Page No. – Page No.  Digging into the Sequential Space of Thiolactone Precision Polymers: A Combinatorial Strategy to Identify Functional Domains |
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