Logical Stimuli-Triggered Delivery of Small Molecules from Hydrogel Biomaterials

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Statement of Purpose: Disease dynamics and the vast benefits of localized therapeutic activity necessitate development of smart drug delivery platforms with biologically defined release profiles. Stimuli-responsive hydrogels provide an isolated aqueous environment that can protect and stabilize its payload until liberation is triggered. Delivery of cargo larger than the gel pores (e.g., cells, proteins) can be obtained through physical entrapment within biodegradable constructs. As unbound small molecules freely diffuse through the hydrogel mesh, their controlled release can be achieved through tethering to non-degradable hydrogels via scissile bonds. While hydrolysable linkers can extend delivery from gels, smart material systems whose cargo release is triggered by specific environmental stimuli may provide new opportunities in personalized medicine.

Towards the advancement of intelligent drug delivery platforms, we recently introduced a modular synthetic strategy to formulate biomaterials that degrade in response to precise combinations of user-defined inputs following Boolean logic[1]. In this approach, stimuli sensitivity is programmed into materials by specifying the molecular connectivity of orthogonal degradable groups within hydrogel crosslinkers. Here, we extend this biocomputational approach to govern the logic-based release of pendant small molecule cargos from non-degradable gels through molecularly defined stimuli-labile linkers (Figure 1).

By varying the molecular architecture of orthogonal stimuli-labile linkages between small molecules and non-degradable materials, we demonstrate the Boolean logic-based release of model therapeutics from gels (Figure 1a). Programmable responses are demonstrated for materials sensitive to input combinations involving enzymes, chemical reductants, and light via YES, OR, and AND logic gates. We anticipate that these platforms will be highly applicable in targeted drug delivery, molecular diagnostics, and tissue engineering.

Methods: Non-degradable hydrogels were formed through a strain-promoted azide-alkyne cycloaddition between a four-arm poly(ethylene glycol) (PEG) tetra-bicyclononyne (M_n ~ 20 kDa) and a linear PEG di-azide (M_n ~ 3.5 kDa)[2]. Hydrogels were functionalized with azide-containing model small molecule therapeutics through disulfide-, –GPQGIWGQ– peptide-, and *ortho*-nitrobenzyl ester-containing linkers that cleave in response to TCEP, MMP-8, and light, respectively. YES-type responsive systems included a single degradable moiety between the gel and cargo; OR-type materials included two in series; AND-type included two in parallel (Figure 1b-c). Gels were treated with all possible combinations of inputs (including no treatment). Small molecule release into gel supernatant was quantified for each pendant type and stimuli combination.

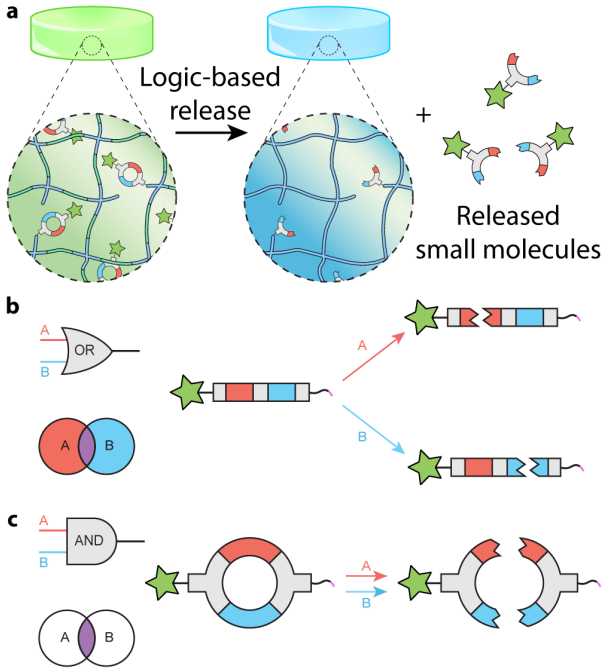

Figure 1. (a) Small molecules conjugated to hydrogel biomaterials through degradable linkages of defined molecular architecture undergo triggered release in response to precise combinations of environmental inputs following Boolean logic. (b) OR-responsiveness is achieved through inclusion of two degradable moieties in series between gel (pink line) and small molecule (green star). (c) AND-responsiveness is achieved through inclusion of degradable groups connected in parallel.

Results: We created and tested seven individual YES-, OR-, and AND-type pendants that release their small molecule cargo in response to complex combinations of inputs following Boolean logic. In each case, small molecule release was enhanced in treatment conditions involving programmed inputs. We used these platforms to demonstrate the sequentially triggered release of small molecules obtained in response to staggered inputs.

Conclusions: This work introduces the first modular strategy to release tethered small molecules in response to precise combinations of user-defined environmental inputs. Though our efforts have focused on polymeric hydrogels sensitive to input combinations of enzymes, chemical reductants, and light, the modularity of the approach – whereby overall response is dictated by the identity and connectivity of various stimuli labile bonds – should enable the creation of a near-infinite number of responsive materials that sense a wide variety of inputs.

References:

1. Badeau B.A. Nature Chemistry. 2018;10;251-258
2. DeForest C.A. Nature Materials. 2015;14:523-531