SUPPORTING information

Beyond the dilemmas: design of PLA-PEG assemblies based on pH-reversible boronic ester for the synchronous PEG de-shielding and ligand presentation to hepatocytes.

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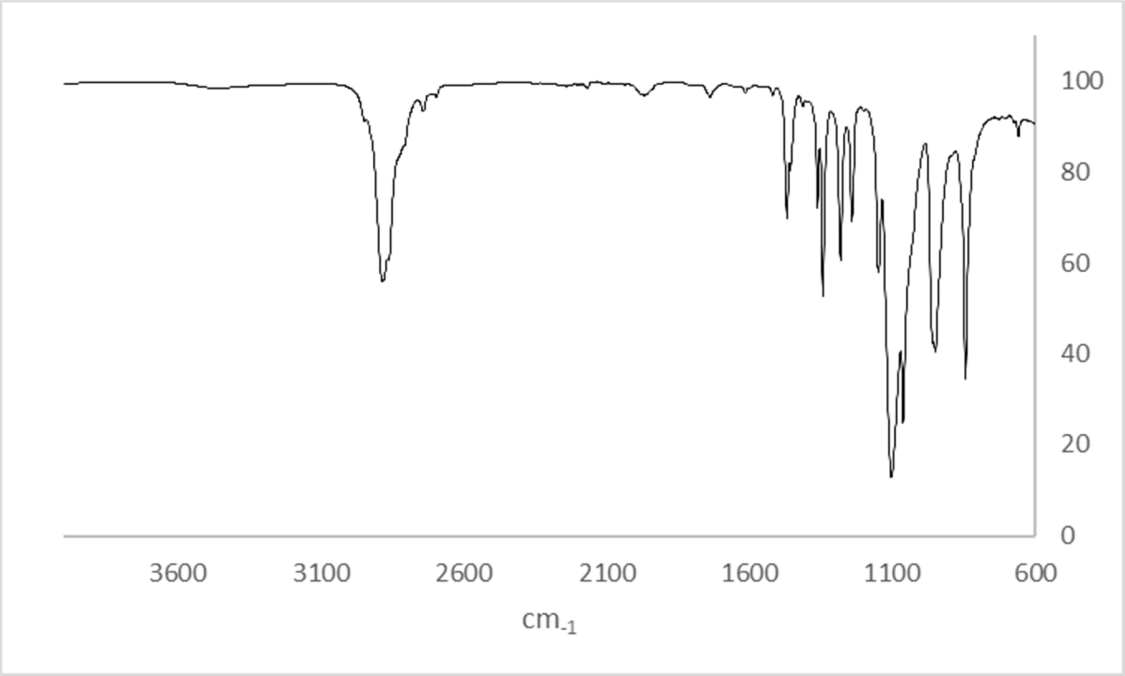


Figure S1. ATR FTIR spectrum of MeO-PEG$_{2000}$-PBA.

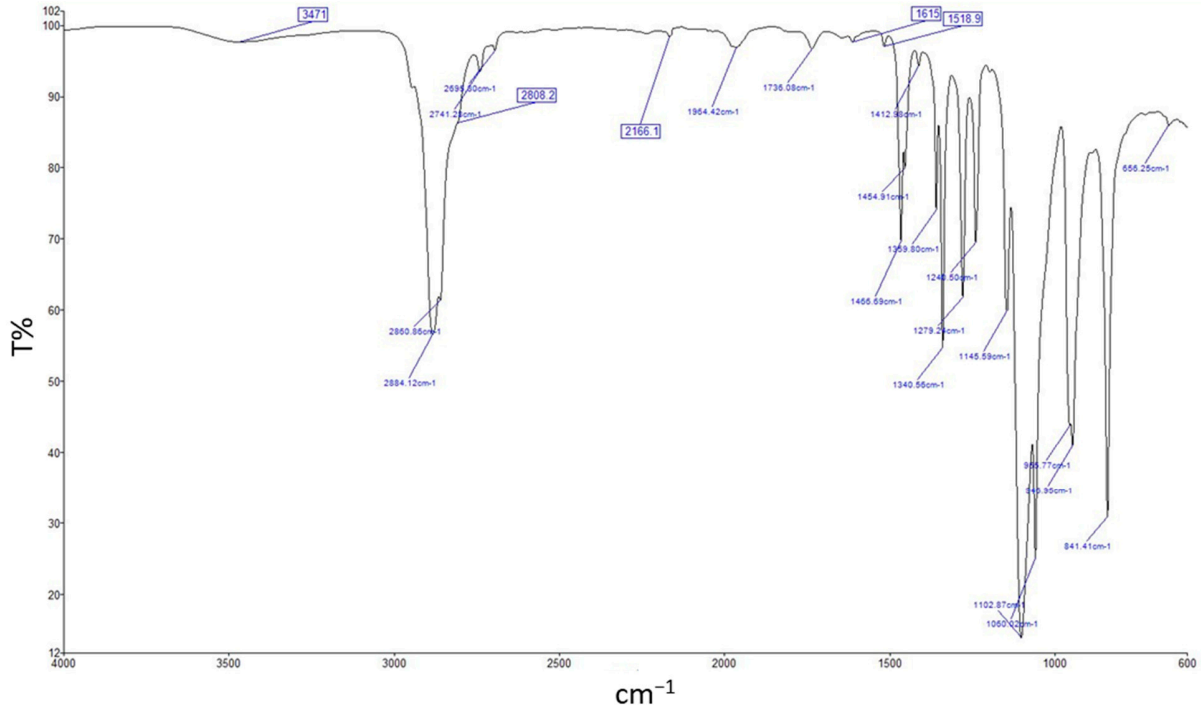


Figure S2. ATR FTIR spectrum of MeO-PEG$_{2000}$-PBA.

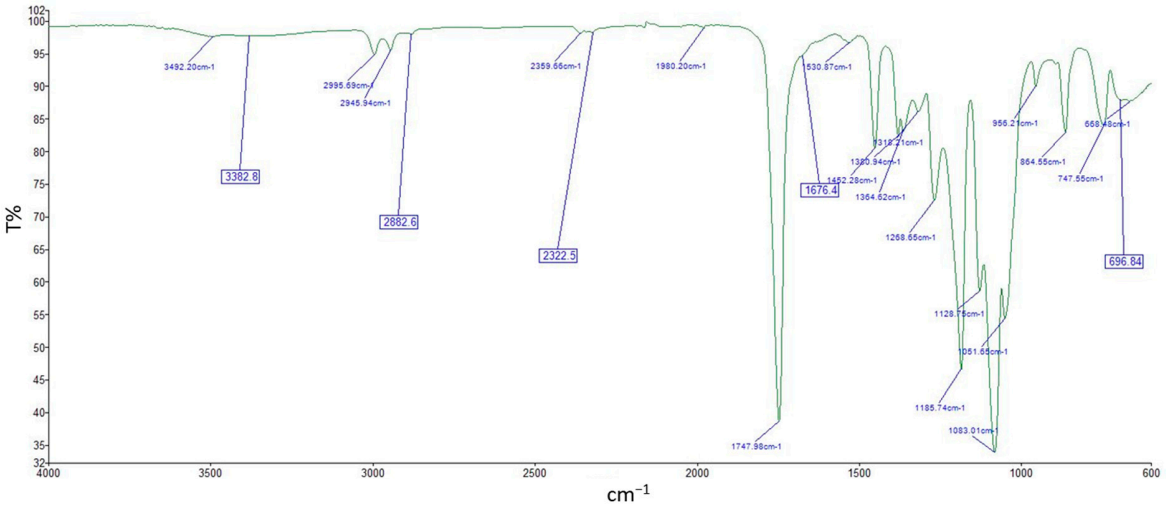


Figure S3. ATR FTIR spectrum of PLA-Alk.

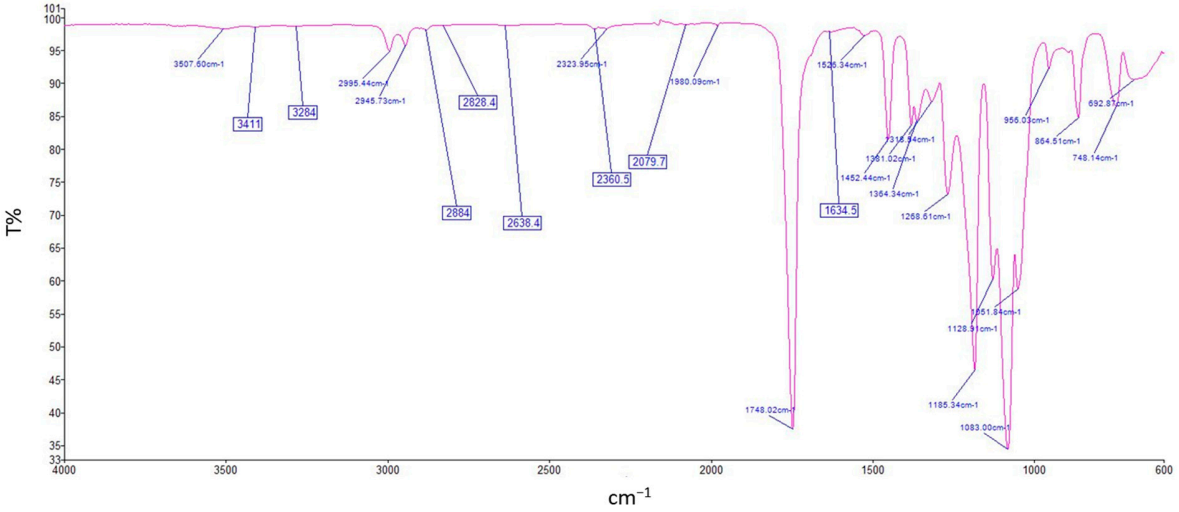


Figure S4. ATR FTIR spectrum of PLA-Gal.

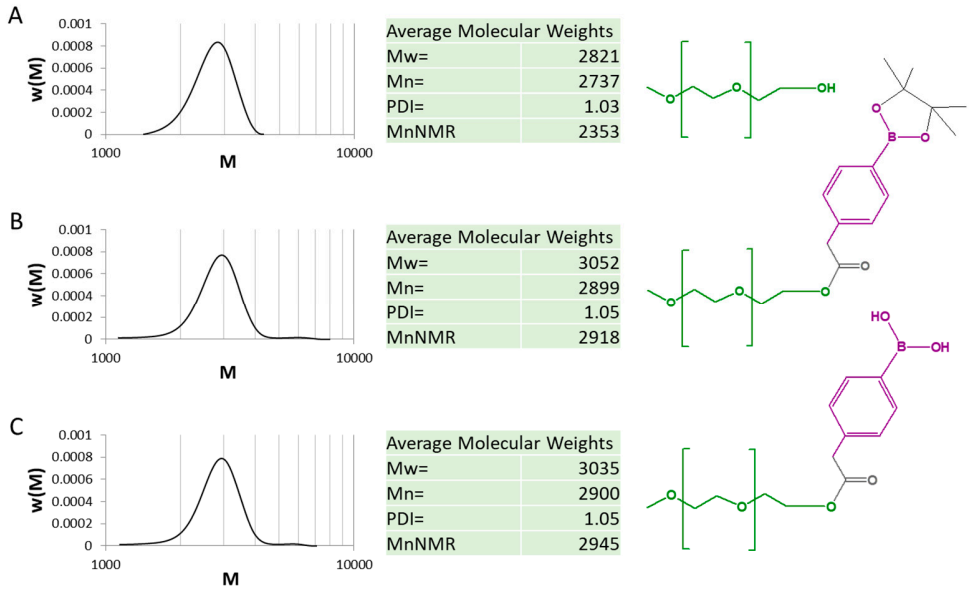


Figure S5. Characteristics of PEG derivatives and their weighted distribution of MW obtained by GPC. A: MeO-PEG_{2000} ; B: MeO-PEG_{2000}-PBAPin; C: MeO-PEG_{2000}-PBA.

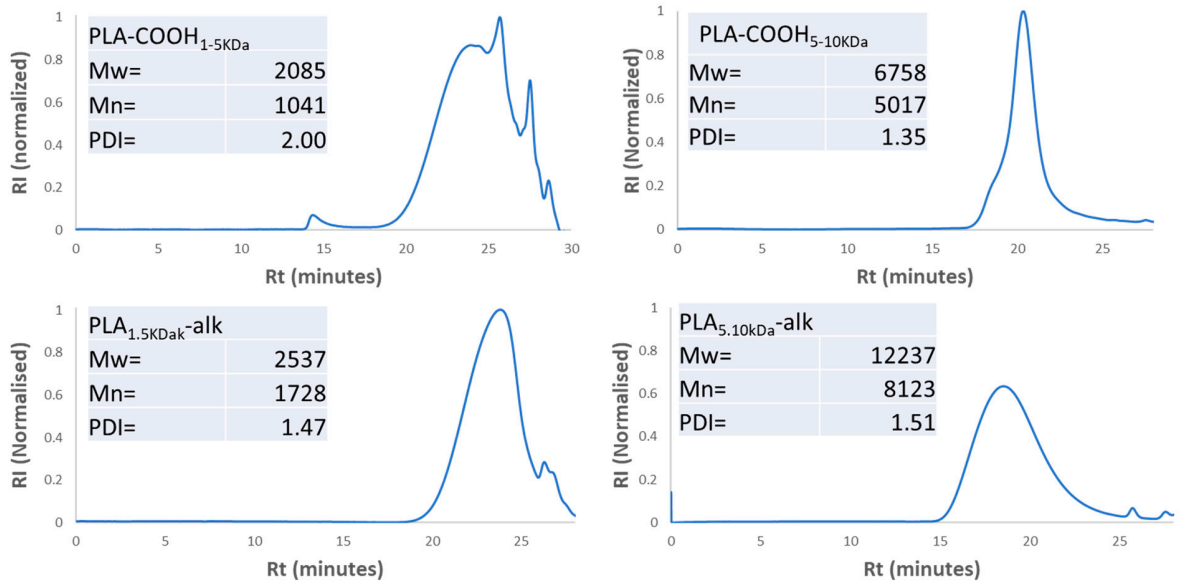
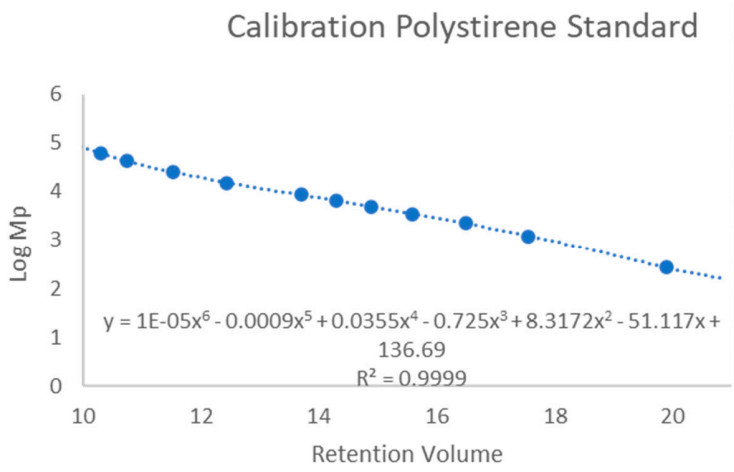


Figure S6. Characteristics of PLA-COOH and their GPC traces.



	V (ml)	Mp
14.709	10.2963	62500
15.353	10.7471	42600
16.483	11.5381	25700
17.765	12.4355	15500
19.564	13.6948	8670
20.414	14.2898	6670
21.266	14.8862	4880
22.267	15.5869	3460
23.561	16.4927	2250
25.074	17.5518	1220
28.434	19.9038	266

Figure S7. Calibration of the GPC system. Processing was carried out according with Gavrilov and Monteiro[16]. Calibration curve with various PEG standards (in the range 600 - 44000 Da) was obtained by polynomial regression, with satisfying correlation coefficients.

Analytical methods used for the calculation of binding constants

At pH 10, for each sample, the amount of complex [AB] was calculated as the difference between initial concentration of ARS (C_{ars}) and the free one at the equilibrium [A], determined by lambert beer law. The binding constant was then obtained by nonlinear regression from *Equation (S1)*:

$$[AB] = \frac{C_{ars} + C_{PEG-PBA} + \frac{1}{K_{ars}} - \sqrt{(C_{ars} + C_{PEG-PBA} + \frac{1}{K_{ars}})^2 - 4C_{ars}\,C_{PEG-PBA}}}{C_{ars}} \qquad (S1)$$

At pH 7.4, being the absorption of ARS overlapped with the one of the complex, the hypsochromic shift of the band was followed with increasing the concentration of MeO-PEG$_{2000}$-PBA (**Figure S8A**). According with Gennari et al.[8], raw data of the spectra of ARS alone and ARS/MeO-PEG-PBA 1:100, taken as the pure complex, were fitted with Gaussian curves (**Figure S8B**).

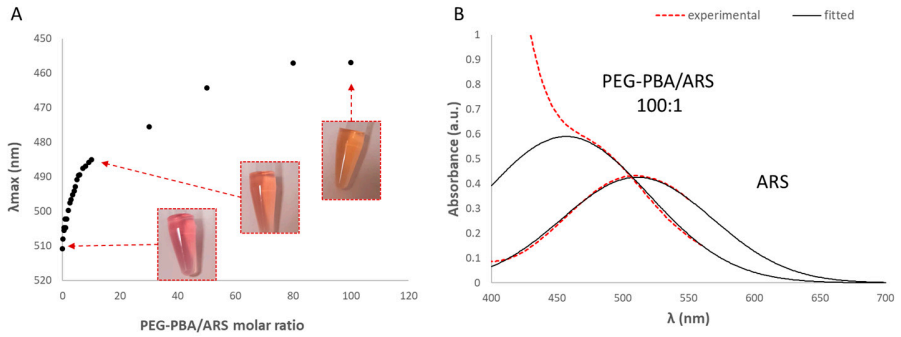


Figure S8. A. Hypsochromic shift of the band around 500 nm with increasing the concentration of MeO-PEG$_{2000}$-PBA in the presence of Alizarin red S at a concentration of $10.2 \cdot 10^{-2}$ mM. B. Experimental and fitted spectra of ARS alone and ARS/MeO-PEG-PBA 1:100. By adding increasing amount of MeO-PEG-PBA to an ARS solution with a fixed concentration, a gradually more intensive orange color was observed, qualitatively suggesting the interaction between ARS and MeO-PEG-PBA (the medium alone, PBS with 1% of DMSO, pH 7.5 didn't produce any shift when mixed with ARS solution, data not shown). Approaching a MeO-PEG-PBA/ARS molar ratio of 100, the shift was constant at 457 nm and the equilibrium shifted towards the ester.

Using a linear combination of those curves (***Equation (S2)***), the spectra for different ARS/APBA mixtures was calculated (**Figure S9A**) and the λ_{max} of the obtained gaussians were plotted versus the free ARS molar fraction, χA (**Figure S9B**). The data fits with a Boltzman distribution (***Equation (S3)***).

$$Abs = \chi A\, C_{ars}\, \varepsilon_{ars} e^{-2\left[\frac{\lambda - \lambda max_{ars}}{\omega_{ars}}\right]^2} + (1 - \chi A) C_{ars}\, \varepsilon_{\frac{ars}{PBA}} e^{-2\left[\frac{\lambda - \lambda max_{\frac{ars}{PBA}}}{\omega_{\frac{ars}{PBA}}}\right]^2} \qquad (S2)$$

$$\lambda_{max} = \frac{(524.47 - 448.42)}{1 + e^{(\chi A - 0.576)/-0.278}} + 448.42 \qquad (S3)$$

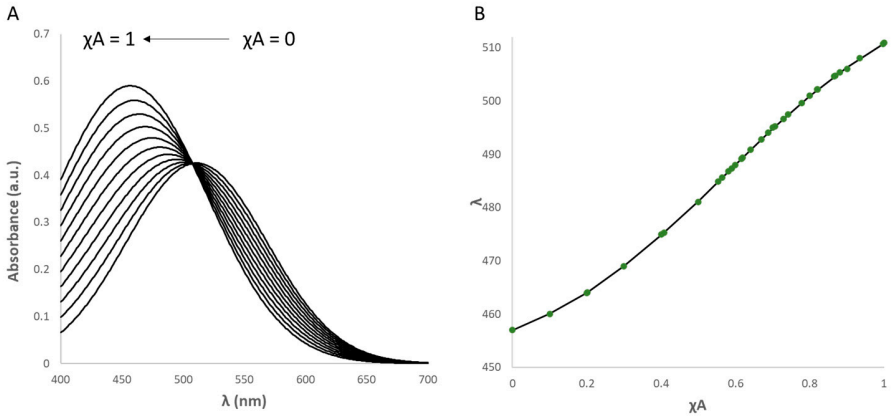


Figure S9. A. Calculated spectra for different ARS/APBA mixtures. B. Boltzman distribution of λ_{max} vs free ARS molar fraction (χA).

Through this master curve, χA was extrapolated for each MeO-PEG$_{2000}$-PBA/ARS and the binding constant (K_{ars}) was then obtained by nonlinear regression from **Equation (S4)**:

$$\chi A = 1 - \frac{[AB]}{C_{ars}} = 1 - \frac{C_{ars} + C_{PEG-PBA} + \frac{1}{K_{ars}} - \sqrt{(C_{ars} + C_{PEG-PBA} + \frac{1}{K_{ars}})^2 - 4C_{ars}\,C_{PEG-PBA}}}{2C_{ars}} \qquad (S4)$$

The gradual addition of Gal to an ARS boronic ester determines the competitive equilibrium AB + D ↔ DB + A which is governed by a constant (Kexc) which can be expressed as the ratio of the two equilibrium constants for the formation of individual boronic esters, AB (Kars) and DB (K_{Gal}), but can also be expressed as a function of the concentration of free ARS as the only variable (see Equations (S5) and (S6)).

$$Kexc = \frac{K_{Gal}}{K_{ars}} \qquad (S5)$$

$$Kexc = \frac{[A](C_{PEG-PBA} - C_{ars} + [A])}{(C_{ars} - [A])\,[C_{Gal} - C_{PEG-PBA} + (C_{ars} - [A])]} \qquad (S6)$$