

# High Molecular Weight Polyacrylamides by Atom Transfer Radical Polymerization: Enabling Advancements in Water-Based Applications

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Received 28 September 2011; accepted 4 October 2011; published online 12 November 2011

DOI: 10.1002/pola.25041

**ABSTRACT:** Through the use of copper (I) chloride (CuCl) and tris(2-dimethylaminoethyl)amine (Me<sub>6</sub>-TREN) as a metal/ligand pair, conditions for the robust, fast, and controlled radical polymerization of high molecular weight *N*-hydroxyethylacrylamide (HEAm), *N*-isopropylacrylamide (NIPAm), *N,N*-dimethylacrylamide (DMAm), and acrylamide (Am) at ambient temperature are reported. Linear evolution of molecular weight and narrow molecular weight distribution was observed for all monomers with degrees of polymerization ranging from 50 to 5000. Random copolymers of several acrylamide-based monomers are also reported with excellent control over molecular weight and polydispersity. Characterization of high molecular weight poly(NIPAm) demonstrated large changes in the lower critical solu-

tion temperature observed on heating and cooling, and this hysteresis was exploited for the controlled release of doxorubicin from poly(NIPAm) spheres. This study represents the first example of preparation of high molecular weight acrylamide polymers by a metal-mediated controlled radical polymerization technique. Access to these materials, as well as to NIPAm polymers in particular, opens new doors for interesting applications in a variety of fields including tissue engineering, drug delivery, and controlled solution viscosity. © 2011 Wiley Periodicals, Inc. *J Polym Sci Part A: Polym Chem* 50: 181–186, 2012

**KEYWORDS:** atom transfer radical polymerization (ATRP); stimuli-sensitive polymers; water-soluble polymers

**INTRODUCTION** Water-soluble and biocompatible acrylamide-based polymers provide an excellent platform for a variety of biomedical applications such as tissue engineering and drug delivery, as well as many industrially relevant processes including use as hydrolytically stable viscosity modifiers, and precipitation and flocculation agents.<sup>[1–4]</sup> In many cases, these acrylamide polymers must have a remarkably high degree of polymerization. Several “controlled” radical polymerization (CRP) (DP) techniques have been developed over the past 15 years leading to exceptional control over targeted molecular weight and providing narrow molecular weight distribution of a wide variety of monomers, which include (meth)acrylates, (meth)acrylamides, styrenics, acrylonitrile, vinyl acetate, and other vinylic monomers.<sup>[5–7]</sup> These methods include atom transfer radical polymerization (ATRP),<sup>[8–11]</sup> nitroxide-mediated polymerization (NMP),<sup>[6,12]</sup> reversible addition fragmentation chain-transfer (RAFT) polymerization,<sup>[6,13,14]</sup> and more recently, single electron transfer living radical polymerization (SET-LRP).<sup>[15–17]</sup> Although the preparation of acrylamide-based polymers has been reported previously using several CRP methods, only one report included the preparation of high molecular weight acrylamide (Am) and *N,N*-dimethylacrylamide (DMAm) polymers ( $M_n > 100$  kDa).<sup>[18]</sup> In this report,  $\gamma$ -irradiation-medi-

ated RAFT polymerization was applied, however,  $\gamma$ -irradiation is not a commonly used technique, because the exotic radiation source is impractical.

Poly(*N*-isopropylacrylamide) (poly(NIPAm)) is a particularly important acrylamide polymer that has garnered considerable attention on account of temperature-dependent solubility in water arising from a temperature-triggered coil-to-globule conformational transition of the polymer chains. At temperatures above the lower critical solution temperature (LCST), the “extended” and well-solvated polymer chains collapse to assume a globular conformation on account of extensive intramolecular hydrogen bonding and hence become immiscible in water.<sup>[19]</sup> This thermoresponsive behavior is a useful property that has been exploited in many applications such as drug delivery, cell immobilization, and chromatographic separation.<sup>[1,2,20–22]</sup> Several examples exist for the preparation of relatively low molecular weight poly(NIPAm) ( $M_n < 40$  kDa). Linear, narrow-dispersed poly(NIPAm) has been prepared by NMP<sup>[23]</sup> and RAFT polymerization<sup>[24,25]</sup>, along with several other acrylamide monomers.<sup>[26]</sup> Additionally, Percec and coworkers have recently reported the Cu(0)wire/CuCl<sub>2</sub>/Me<sub>6</sub>-TREN-mediated SET-LRP of NIPAm and DMAm.<sup>[27]</sup>

Additional Supporting Information may be found in the online version of this article.

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The successful ATRP of NIPAm and other acrylamide monomers in water, alcohols, and mixtures of water and organic solvents using CuCl/Me<sub>6</sub>-TREN as a catalytic system has also been described.<sup>[28–34]</sup> Although these reports have primarily used Cu(I) for the polymerization of various acrylamide polymers citing the ATRP mechanism, the exact mechanism of polymerization has been disputed in the literature.<sup>[15,35]</sup> According to Percec et al., disproportionation of Cu(I) is expected under these polymerization conditions on account of the highly polar nature of the solvents and the particular ligand used.<sup>[15,16]</sup> Under the SET-LRP mechanism, Cu(0) triggers activation of a halide-containing initiator for generation of radical species and Cu(II) works as a deactivator to cap the propagating radical species. However, ATRP may indeed be the predominant mechanism in these polymerizations whereby Cu(I) is the primary activating species and Cu(0), resulting from disproportionation of the Cu(I) species under these conditions, can act as a reducing agent for the regeneration of Cu(I) activator from Cu(II) according to the mechanism of activators (re)generated by electron transfer ATRP (A(R)GET-ATRP).<sup>[35–39]</sup> Additionally, ATRP has been performed previously in water and water/alcohol mixtures.<sup>[40–43]</sup> In any case, it is possible for both ATRP and SET-LRP mechanisms to contribute to controlled radical polymerization in water and in alcohol/water mixtures.<sup>[44]</sup>

The recent success of both SET-LRP and ARGET-ATRP at producing high molecular weight (meth)acrylate polymers provided motivation to pursue a copper-mediated radical polymerization route (a much more accessible approach than  $\gamma$ -irradiation) for the preparation of high molecular weight acrylamide-based (co)polymers.<sup>[17,27,38]</sup> Herein, we describe a facile, robust, and fast synthetic protocol using ATRP allowing for the controlled preparation of acrylamide-based (co)polymers over a wide range of molecular weights ( $M_n = 5000$ – $500,000$  Da). The thermoresponsive behavior of NIPAm-containing (co)polymers was investigated, and the utility of the polymers for molecular-weight-dependent con-

**TABLE 1** Polymerization of Acrylamides Using CuCl/Me<sub>6</sub>-TREN

Entry	Monomer	$[M]_0/[I]_0$	$M_n$ (kDa) <sup>a</sup>	PDI <sup>a</sup>
1 <sup>b</sup>	NIPAm	50	6.8	1.08
2 <sup>b</sup>	NIPAm	500	56	1.06
3 <sup>b</sup>	NIPAm	5,000	590	1.49
4 <sup>b</sup>	DMAm	50	5.5	1.05
5 <sup>b</sup>	DMAm	500	41	1.08
6 <sup>b</sup>	DMAm	5,000	245	1.14
7 <sup>c</sup>	HEAm	50	5.8	1.08
8 <sup>c</sup>	HEAm	500	59	1.09
9 <sup>c</sup>	HEAm	5,000	440	1.23
10 <sup>d</sup>	Am	50	3.5	1.10
11 <sup>d</sup>	Am	500	48	1.16
12 <sup>d</sup>	Am	5,000	365	1.10

<sup>a</sup> Determined by GPC using H<sub>2</sub>O as eluent.

<sup>b</sup> EtOH:H<sub>2</sub>O (80:20).

<sup>c</sup> EtOH:H<sub>2</sub>O (50:50).

<sup>d</sup> EtOH:H<sub>2</sub>O (30:70).

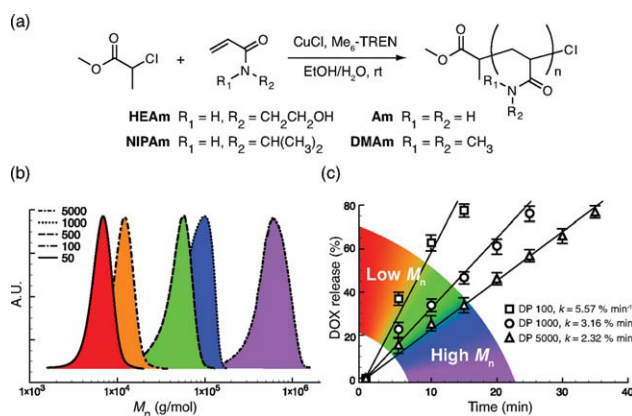
trol over the sustained release of doxorubicin, an important anticancer therapeutic, from polymer particles is described.

## RESULTS AND DISCUSSION

Initially, the polymerization of NIPAm was performed using MCP:CuCl:Me<sub>6</sub>-TREN (1:1:1) in a mixture of ethanol and water. It was determined that the polymerization of NIPAm is dependent on solvent composition with an optimal composition of ethanol:water (80:20) (see Table S1, Supporting Information). The polymerization was performed at ambient temperature and no induction period was observed. A detailed kinetic study was performed with a targeted DP of 500, and the polymerization reaches > 98% conversion in 70 min ( $k_p^{app} = 0.0201 \text{ min}^{-1}$ ) with high initiator efficiencies ( $I_{eff} = 98\%$ ) and yields a polymer with a low polydispersity ( $M_w/M_n < 1.2$ ). The low polydispersity index (PDI) supports the absence of undesired side-reactions and the controlled nature of the polymerization. Additionally, experimentally obtained molecular weights of the purified polymers are in accordance with the targeted molecular weights across a wide range of DPs  $[NIPAm]_0/[MCP]_0 = 50$ – $5000$ , and their GPC traces are shown in Scheme 1(b) (also see Fig. S1, Supporting Information).

To test the generality of the polymerization conditions for other acrylamide polymers, they were applied to the controlled polymerization of DMAm.<sup>[27,45]</sup> Polymerization of DMAm in ethanol/water (80:20) ( $[MCP]_0:[CuCl]_0:[Me_6-TREN]_0$  ratio of 1:1:1), provided control over a wide range of targeted molecular weights (DP = 50–5000, Table 1). The reaction rates ( $k_p^{app} = 0.047 \text{ min}^{-1}$ ) were comparable to the polymerization of NIPAm and high conversions (>98%) were observed with low polydispersities ( $M_w/M_n < 1.2$ ) regardless of the  $[DMAm]_0/[MCP]_0$  ratio.

N-Hydroxyethylacrylamide (HEAm) is another important water-soluble monomer with the added advantage that it contains a hydroxyl group providing pendant functionality in



**SCHEME 1** (a) Synthetic scheme for the polymerization of HEAm, Am, NIPAm, and DMAm. Demonstration of (b) high range of poly(NIPAm) molecular weights attainable and (c) the subsequent control over release of DOX from poly(NIPAm) particles.

**TABLE 2** Random Copolymerization of Acrylamides Using the CuCl/Me<sub>6</sub>-TREN Catalytic System with [M]<sub>0</sub>:[MCP]<sub>0</sub>:[CuCl]<sub>0</sub>:[Me<sub>6</sub>-TREN]<sub>0</sub> = 500:1:1:1

Entry	Monomer A	Monomer B	Target B (%)	Experimental B <sup>a</sup> (%)	M <sub>n</sub> <sup>b</sup> (kDa)	PDI <sup>b</sup>
1	NIPAm	HEAm	10	12.7	56	1.15
2	NIPAm	HEAm	20	22.2	47	1.18
3	NIPAm	HEAm	30	31.7	56	1.17
4	NIPAm	HEAm	50	52.4	66	1.16
5 <sup>c</sup>	NIPAm	DMAm	10	17.7	85.1	1.22
6 <sup>c</sup>	NIPAm	DMAm	20	32.0	65.8	1.17
7	HEAm	Am	50	52.5	47.2	1.16

<sup>a</sup> Determined by <sup>1</sup>H NMR.

<sup>b</sup> Determined by GPC using H<sub>2</sub>O as eluent.

<sup>c</sup> [M]<sub>0</sub>:[MCP]<sub>0</sub>:[CuCl]<sub>0</sub>:[Me<sub>6</sub>-TREN]<sub>0</sub> = 1,000:1:1:1.

the corresponding polymer. This functionality is compatible with myriad postpolymerization functionalization techniques including esterification, etherification, and isocyanate coupling.<sup>[46]</sup> The CRP of HEAm has been reported previously utilizing the CuCl/Me<sub>6</sub>-TREN catalyst/ligand system with ethyl 2-chloropropionate as initiator in alcohol/water mixtures.<sup>[47–49]</sup> However, in these few reports only low molecular weight polymers were obtained ( $M_n < 20$  kDa). The conditions for polymerization of NIPAm and DMAm could be applied to HEAm with only a slight change in the solvent composition. When ethanol/water (80:20) was applied directly, the resulting polymers had broadened polydispersities and did not reach the targeted molecular weights (Table S2, Entry 1, Supporting Information). Additionally, mixtures containing a higher water content (70%) yielded polymers with high polydispersity and loss of control over the polymerization (Table S2, Entry 2, Supporting Information). Optimal solvent composition was determined to be ethanol/water (50:50), and the higher water content yielded much faster polymerizations than those observed in the polymerization of both NIPAm and DMAm (Table 1), which is consistent with previously observed trends.<sup>[15,16]</sup> For a targeted DP of 500, the polymerization reached 80% conversion in 10 min ( $k_p^{\text{app}} = 0.154 \text{ min}^{-1}$ ). Although the polydispersities are relatively high at low conversion, they decrease throughout the polymerization, resulting in polymers with very low polydispersities ( $M_w/M_n < 1.1$ ), regardless of the [HEAm]<sub>0</sub>/[MCP]<sub>0</sub> ratio.

To demonstrate the robust nature of the polymerization conditions, HEAm was also polymerized using various liquors as solvent, including vodka and zivania, removing the necessity for the preparation of the solvent mixtures.<sup>[50,51]</sup> In each case, even when low quality liquors were used, the polymerization proceeded in an identical manner as when the ethanol:water mixtures were prepared from absolute ethanol and distilled water.

Following the previous success with the ATRP of the aforementioned monomers, poly(acrylamide) of a wide range of targeted DPs was prepared. Poly(acrylamide) has been polymerized previously by NMP and RAFT.<sup>[18,52,53]</sup> Ethanol/water

(30:70) yielded optimal control over the targeted molecular weights (Table 1, Entries 10–12), and the polydispersities remained low ( $M_w/M_n < 1.2$ ) throughout the duration of the polymerization. Again, no induction period was observed, and high conversions were reached rapidly (70% conversion in 10 min) under these conditions, as the rate of polymerization is high ( $k_p^{\text{app}} = 0.130 \text{ min}^{-1}$ ).

In addition to the polymerization of various homopolymers, the current method was extended to the preparation of several random copolymers. On account of the broad utility and applicability of poly(NIPAm) in a variety of fields, copolymers of NIPAm with both DMAm and HEAm were prepared. It has been demonstrated previously that copolymerization of NIPAm with various monomers allows for modulation of the thermoresponsive behavior of the resulting NIPAm-containing (co)polymers (Table 2).<sup>[19,54]</sup> In all cases, the polymerization conditions were identical to those used for the preparation of poly(NIPAm) homopolymers of ethanol/water (80:20). The copolymerization of NIPAm with both HEAm and DMAm was readily achieved over a large molecular weight range producing polymers with excellent control over targeted molecular weight with low polydispersities. The copolymerization of DMAm with NIPAm exhibited slightly higher loading of DMAm than expected (see Supporting Information), likely on account of reactivity differences between the two monomers.

Additionally, copolymerization of HEAm and Am using HEAm homopolymerization conditions of ethanol/water (50:50) was performed. These ATRP conditions were successful for the copolymerization and demonstrated the preparation of acrylamide-based polymers bearing latent hydroxyl functionality pendant from the HEAm comonomer (useful for post-polymerization functionalization methods, as mentioned previously).<sup>[46]</sup>

As NIPAm containing (co)polymers of a broad range of molecular weights and chemical compositions were available, a systematic study of their thermoresponsive behavior in water (Table 3) was undertaken. A strong trend was apparent in the poly(NIPAm) homopolymers as the LCST upon heating (LCST<sub>heating</sub>) clearly decreased from 43 to 32°C

**TABLE 3** LCST Characterization of Poly(NIPAm) Homopolymers and [Random Poly(NIPAm-*co*-HEAm) Copolymers in Water

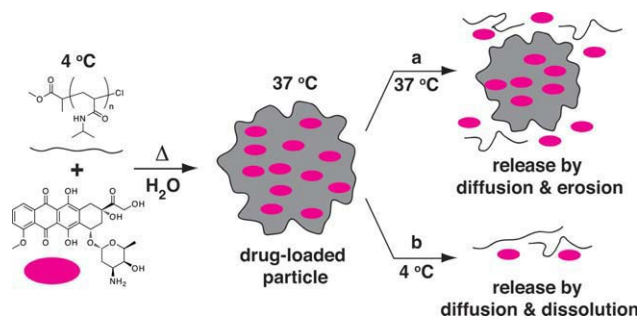
Entry	$M_n$ (kDa) <sup>a</sup>	$F_{\text{NIPAm}}$	$\text{LCST}_{\text{heating}}$ (°C) <sup>b</sup>	$\Delta\text{LCST}$ (°C) <sup>c</sup>
1	6.8	1	43.0	1.2
2	12	1	34.2	4.3
3	56	1	32.2	5.4
4	99	1	31.9	8.2
5	590	1	31.9	9.8
6	56	0.9	42.7	4.0
7	47	0.8	49.1	3.9
8	56	0.7	58.1	4.2
9	66	0.5	– <sup>d</sup>	– <sup>d</sup>

<sup>a</sup> Determined by <sup>1</sup>H NMR.<sup>b</sup> Determined by turbidimetry at a heating rate of 0.2 °C/min and temperature values are taken from transmittance at 50%.<sup>c</sup>  $\Delta\text{LCST} = \text{LCST}_{\text{heating}} - \text{LCST}_{\text{cooling}}$ .<sup>d</sup> LCST not observed for this polymer.

(Table 3, Entries 1–5) as molecular weight increased up to 50 kDa, which is in agreement with previous findings.<sup>[54]</sup> Additionally, all of the polymers demonstrated hysteresis between their heating and cooling profiles (at a rate of 0.2 °C/min). This hysteresis ( $\Delta\text{LCST} = \text{LCST}_{\text{heating}} - \text{LCST}_{\text{cooling}}$ ) increases with the molecular weight on account of a more entangled hydrophobic domain in the higher molecular weight materials, thus requiring more time to reestablish a well-solvated and extended conformation, resulting in a lower observed  $\text{LCST}_{\text{cooling}}$ . A logarithmic relationship exists between the polymer molecular weight and the observed hysteresis value (Fig. S11, Supporting Information), however, further probing of this relationship is outside the scope of this report.

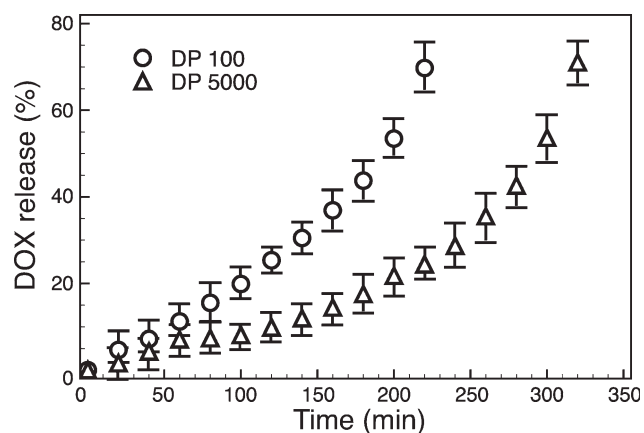
The random poly(NIPAm-*co*-HEAm) copolymers demonstrated a linear increase in LCST as a function of HEAm monomer incorporation up to 50% at which point no thermoresponsive behavior was observed. However, the hysteresis value for the random copolymers remained constant around 4 °C for all loadings of HEAm comonomer, as the DP remained constant at 500. Coupled with the trend observed for the poly(NIPAm) homopolymers, the hysteresis is more strongly correlated to the molecular weight of the (co)polymer. Although the  $\text{LCST}_{\text{heating}}$  is determined by both the polymer chemical composition and the polymer molecular weight. It is therefore possible to finely tune both the observed LCST and any hysteresis existing between heating and cooling by controlling both the chemical composition and the molecular weight of NIPAm-containing polymers.

The large variation in LCST behavior (the observed hysteresis) of the polymers at high molecular weights suggested that an enhanced release profile of an important hydrophobic chemotherapeutic drug, doxorubicin (DOX), could be achieved from polymer particles formed at physiological temperature. DOX-loaded polymer spheres were prepared and stabilized at 37 °C and the release of the drug was monitored over time [Scheme 2(a)]. Figure 1. clearly shows a dramatic increase from 200 to more than 300 min for total release of DOX from

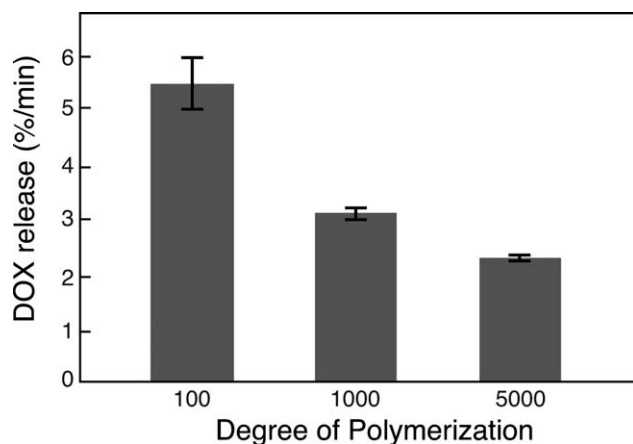
**SCHEME 2** Schematic representation of the encapsulation of DOX into poly(NIPAm) particles and the subsequent release of the drug through (a) diffusion and erosion at physiological temperature or (b) dissolution and subsequent release (cartoons are not drawn to scale).

particles prepared from high molecular weight poly(NIPAm) ( $M_n = 500$  kDa) when compared with those from smaller poly(NIPAm) ( $M_n = 10$  kDa), demonstrating a clear molecular weight dependence. The release profile, however, was anomalous and did not fit Fickian diffusional release according to the Ritger–Peppas equation.<sup>[55,56]</sup> The release profile was likely a composite of diffusion of DOX molecules from the hydrophobic domains and erosion of the polymer particles.

In addition to measuring the release of DOX at 37 °C where the particles remain hydrophobic, a second study was performed at lower temperatures to demonstrate the molecular weight dependence of the dissolution of the particles and subsequent release of the drug. DOX-loaded polymer particles were prepared and stabilized at 37 °C and then rapidly cooled to 4 °C in water. Scheme 1(c) and Figure 2 show that the release profile of the drug from these particles has a large molecular weight dependence as the larger poly(NIPAm) polymers yielded a much slower release of the DOX drug. The release kinetics decrease as the molecular weight increases and a logarithmic relationship exists between them (Fig. S13, Supporting Information), which parallels the relationship observed previously (Table 3 and Fig. S11,

**FIGURE 1** DOX release profile from poly(NIPAm) particles at 37 °C.





**FIGURE 2** DOX release rate from poly(NIPAm) particles in water at 37 °C.

Supporting Information) between the hysteresis in the LCST behavior of the polymers and their molecular weight. The correlation between the polymer LCST behavior and the DOX release kinetics from the corresponding particles clearly demonstrates that the release profile is highly tunable through control over polymer characteristics afforded by the facile and robust ATRP conditions described above.

## CONCLUSION

In summary, we have demonstrated that controlled ATRP of high molecular weight acrylamide-based monomers over a wide range of molecular weights (DP = 50 – 5000) can be carried out in ethanol/water mixtures at ambient temperature. The generalized polymerization conditions offer facile and fast preparation of these polymers. Access to these materials, as well as to NIPAm-containing (co)polymers in particular, enables applications in a variety of fields including tissue engineering, drug delivery, and controlled solution viscosity. Specifically, the preparation of a wide range of molecular weights and chemical compositions for NIPAm-based (co)polymers allows for facile manipulation of the thermoresponsive behavior of these materials in water. Both the observed LCST<sub>heating</sub> and the hysteresis between heating and cooling can be readily tuned, which has been shown to have strong implications for the controlled release of DOX from polymer particles at physiological temperature.

This study was supported in part by Schlumberger, the Walters-Kundert foundation, and an ERC Starting Investigator grant (ASPiRe). X.J. Loh thanks A\*STAR for a postdoctoral fellowship and J.d.B. acknowledges support from the EU through a Marie Curie Intraeuropean Fellowship (FP7-PEOPLE-2010-IEF-273807) within the EC Seventh Framework Programme.

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