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# Physiological Temperature Has Crucial Role in Amyloid Beta in the Absence and Presence of Hydrophobic and Hydrophilic Nanoparticles

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**ABSTRACT.** Amyloid beta fibrillation can lead to major disorder of neurons processes and is associated with several neuronal diseases (*e.g.* Alzheimer's disease). We report here an importance of slight temperature changes, in the physiological range (35-42°C), on the amyloid fibrillation process in the presence and absence of hydrophilic (silica) and hydrophobic (polystyrene) nanoparticles (NPs). The results highlight the fact that slight increases in temperature can induce inhibitory and acceleratory effects of hydrophobic and hydrophilic NPs on the fibrillation process, respectively. Using further *in vivo* considerations, the outcomes of this study can be used for considerable modifications on the current diagnosis and treatment approaches in amyloid-involved diseases.

**KEYWORDS.** amyloid beta, fibrillation, physiological temperature, hydrophilic NPs, hydrophobic NPs,

## Introduction

The misfolding of amyloid-proteins (e.g. amyloid beta (A $\beta$ ) peptide(1-4), prion protein(5),  $\alpha$ -synuclein(6), polyglutamine(7), glucagon(8), and  $\beta$ 2-microglobulin(9, 10)) followed by their fibrillation is the hallmark of over 40 human diseases, ranging from neurodegenerative disorders (e.g. Alzheimer's disease, Parkinson disease, creutzfeld jakob and Gerstmann straussler scheinker syndrome) to non-neuropathic disorders (e.g. Amyloid Heart disease, Rheumatoid arthritis, and type II diabetes).(11, 12) Among various amyloidogenic proteins, A $\beta$  peptides are widely used as model proteins to investigate the effect of NPs on fibrillogenesis.(13) Monomeric A $\beta$  is actually soluble in a physiological condition and has shown to be unstructured(14); however, the fibrillar form has a characteristic cross- $\beta$  structure with stacking of  $\beta$  strands perpendicular to the long axis of the fiber(15-17).

It is well recognised that nanoparticles (NPs) have significant effect on the fibrillation process.(18-20) Interestingly, it was very recently found that NPs with protein corona (protein/biomolecular coated nanoparticles in biological medium(21)) can slow amyloid fibrillation process(22). Although there are few reports on the effect of temperature on the kinetics of amyloid fibrillation process (23-26), a crucial effect of slight temperature changes (*i.e.* in the physiological range) on the amyloid fibrillation process in the presence of NPs has not been investigated. This point is very important for the *in vivo* NP application to humans, specifically for treatment of amyloid proteins (e.g. Alzheimer's- and Parkinson's-disease)(27). The local temperature in different brain diseases/tumors for different individuals is in the range from 33.4 to 42.0 °C.(28-32) In normal body, the body temperature, during the sleep, decreases and manual work leads to an increase of up to 2°C. This means that the body temperature for healthy humans varies in the range from 35 to 39 °C and can find a maximum of 42°C in the case of fever.(33) Although there are significant reports on the effects of various NPs on the amyloid fibrillation process(34-38), as far as we know, there is no report on the effects of slight temperature changes, in physiological range, on the interactions between NPs and A $\beta$ ; thus, we focused our attention on the effects slight temperature changes have on the amyloid fibrillation in the absence

and presence of two commercially available and compositionally different NPs (i.e. “hydrophobic” carboxylated polystyrene NPs and hydrophilic silica). It is notable that we employed these particular NPs because of their importance as the first group of materials, which were evaluated for safety at the nanoscale.(39-41)

## **Results and Discussion**

The amino acid sequence of 17-24 (i.e. KLVFFAED) is known to form amyloids on its own, and most likely has a crucial role in the fibrillation process;(38) thus, we used both molecular dynamic (MD) simulation methods and experimental methods, against monoclonal antibody, to detect the availability/exposure of this sequence at various physiological temperatures (see Figure 1). According to the results, one can observe that by increasing the temperature from 37-42°C, the availability/exposure of KLVFFAED sequence in amyloid backbone is improved. In the next step, using Thioflavin T (ThT) assay, we probed the exposure of the exposed hydrophobic sequence of A $\beta$  with both hydrophilic and hydrophobic NPs, at various temperatures, respectively (see Figure 2 for detail); as seen, the lag time for the pure A $\beta$  (i.e. in the absence of NPs) is decreased gradually, by increasing the temperature from 37-42°C; this happened due to the fact that the core part of fibrillation process (i.e. KLVFFAED sequence) is exposed to each other resulting in faster formation of amyloid oligomers. Both polystyrene and silica NPs had acceleration effects on the fibrillation process at 37°C, however, the most striking observation is that dual effects were observed at higher temperature (i.e. 42°C). More specifically, the acceleration effect of silica NPs was significantly enhanced by increasing the temperature; in contrast, the polystyrene NPs demonstrated strong inhibitory effects on fibrillation process by slight temperature enhancement. The possible mechanism (see Figure 3) for the observed dual effects of various NPs at the same conditions may strongly relate to the surface properties of NPs. For silica NPs (i.e. hydrophilic), the hydrophilic part of A $\beta$  monomers would be attached to the surface of silica NPs, resulting in placement of hydrophobic site in the outer shell of NPs; by increasing temperature, the availability of these hydrophobic sites would be increased, causing the enhancement in acceleration effect on the fibrillation process. In contrast, hydrophobic NPs (i.e. polystyrene NPs) tend to bind with the

hydrophobic part of A $\beta$  monomers, which are more available at higher temperature; thus, the concentration of hydrophilic sites in the outer shell of polystyrene NPs would be increased by increasing the temperature; in this case, one can conclude that the increasing in the interaction temperature can induce considerable inhibitory effect on the hydrophobic NPs. In order to further confirmation on the proposed mechanism, the transmission electron microscopy (TEM) method was employed for the interaction temperature of 42°C. Quiet remarkably, TEM images (see Figure 3) were in good agreement with the schemes and they illustrated the formation of fibrils at the surface of silica NPs; these fibrils were drastically enhanced by increasing the interaction time. In contrast, there was no trace of fibrillation on the polystyrene NP batch at 42°C.

Molecular dynamic simulations (see SI) were performed to probe the underlying mechanism of the observed results. The results, in various temperatures, clearly show time dependence of the molecule structure as it is expected. Figure S1 of SI shows the atomic root mean square displacement (RMSD) of the amyloid structure from the initial state in the simulations. The average radius of gyration of the molecule also confirms structural deformations and also shows that the molecule has the most compact form on 37°C (see Figure S2 of SI). To calculate the radius of gyrations, last 25 ns of any run are considered. Comparing the RMSD from average configuration on 37°C also shows large deviations on 42°C and 27°C which indicates both hot and cold denaturation (see Figure 4a). In the simulations with more than one molecule (2 and 4) we clearly see that the molecules in higher temperatures bind each other faster and stronger. The range of the investigated temperatures spans about 5% temperature difference. The effect of such temperature change on diffusion of the molecule cannot explain the observed change on the speed of fibrillation process and its dynamics. Looking at distance between center of mass of the molecules (Figure S3 of SI), one can see that the molecules approach each other almost in the same time, but their equilibrium distance is smaller in higher temperature. The effect of temperature on the dynamics of fibrillation is also investigated by the mean of all atom simulations (see SI for full detail). Figure 4b shows that an aggregation of four amyloids is formed not only faster in higher temperatures, but also it is more compact there. This is more interesting when we know from

single molecule simulations that the molecule in these two temperatures is swollen in compare to its physiological temperature, almost with the same degree (see Figures 4 a and S2 of SI).

## **Conclusion**

We have reported here a crucial ignored factor (i.e. slight changes in the physiological range) on the protein fibrillation mechanisms in the presence and absence of NPs. From both experimental and simulation methods, it was revealed that the core hydrophobic backbone of A $\beta$  monomers can be more available for interactions by increasing the temperature from 37°C to 42°C. It is also found that hydrophobic NPs (i.e. polystyrene) have capability to show dual effects (i.e. acceleratory and inhibitory) on fibrillation process by slight temperature enhancement; however, for hydrophilic NPs (i.e. silica) the acceleratory effects on the fibrillation process can be significantly increased. These findings need *in vivo* considerations in the future.

Supporting Information: Experimental and simulation details. This information is available free of charge via the Internet at <http://pubs.acs.org/>.

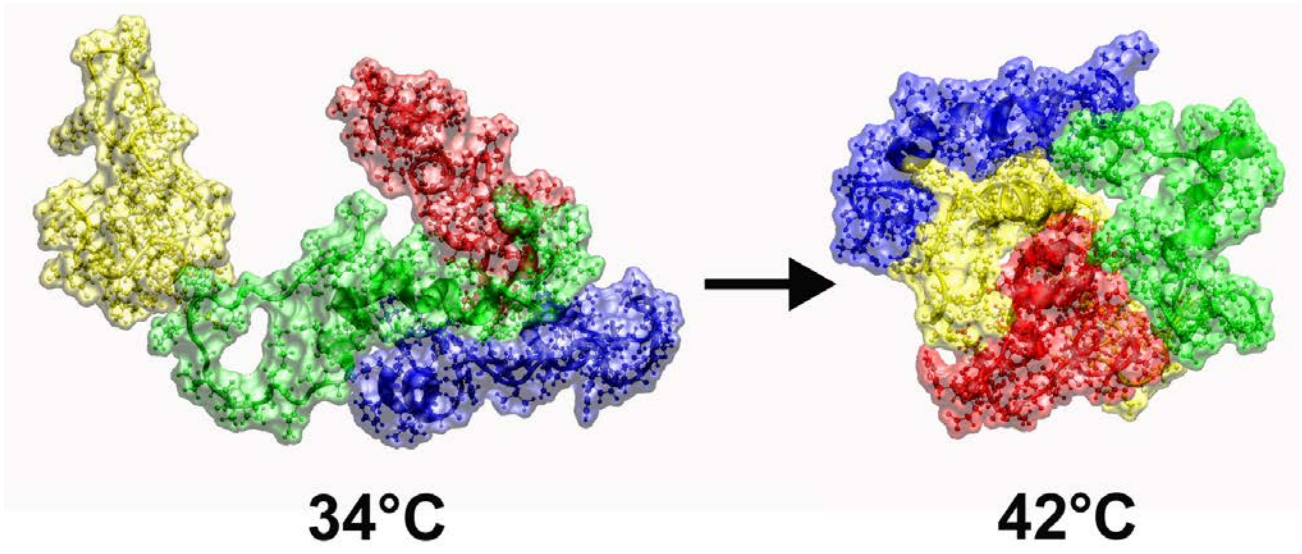
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TOC



## Figure captions

**Figure 1:** Antibody affinity towards hydrophobic section of A $\beta$  at various temperatures.

**Figure 2:** Kinetics of A $\beta$  fibrillation (concentration of 5  $\mu$ M) with and without NPs at temperatures of 37° and 42°C.

**Figure 3:** TEM images of (a) polystyrene and (b) silica NPs with various magnifications, showing the existence of spherical NPs with narrow size distribution. (c) and (d) Representative schemes showing the exposure of the amyloids' hydrophilic and hydrophobic back bone to the free amyloid monomers after interaction with polystyrene and silica particles at 42°C, respectively. (e) and (f) TEM images of the amyloid interacted proteins with polystyrene and silica particles at 42°C, respectively; as seen, there is no trace of fibrillation in (e) however, severe fibrillation (see red arrows as example) were observed in (f); in (e) and (f) left and right images corresponded to interaction of amyloid with nanoparticles at 20 min and 400 min, respectively; scale bar is 100 nm.

**Figure 4:** (a) Average RMSD of amyloid structure from mean configuration on 37°C (protein conformations at defined temperatures were shown). (b) Average distance between the centers of mass of 4 amyloids in 34°C (blue line) and 42°C are varying in temperature in different ways (green line).

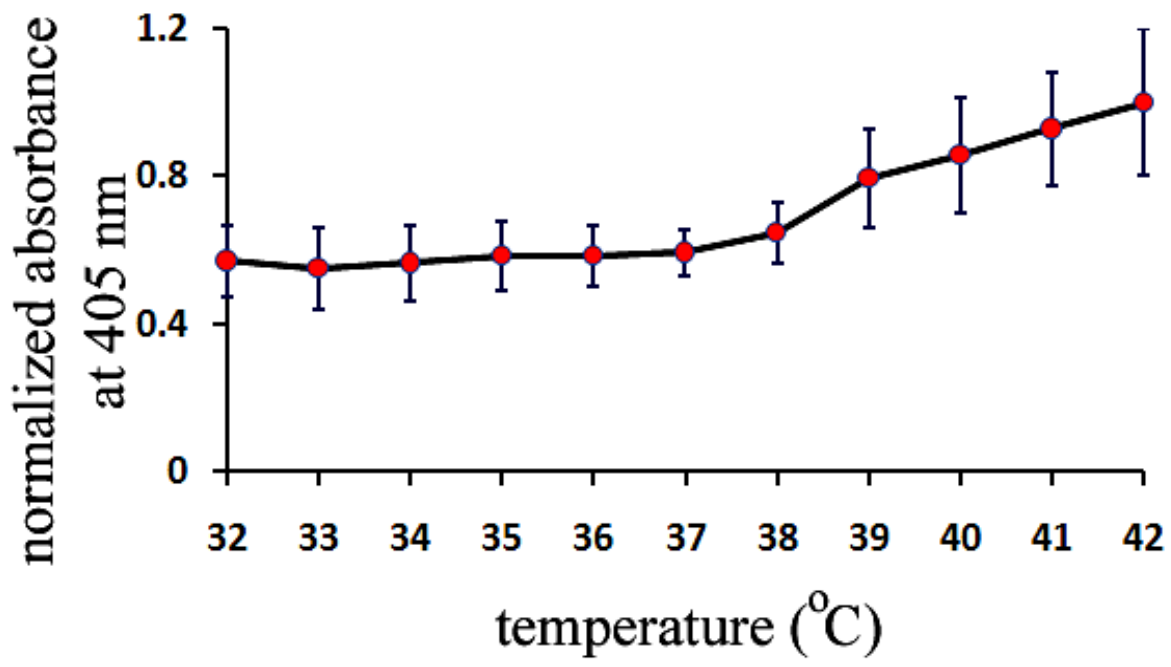


Figure 1

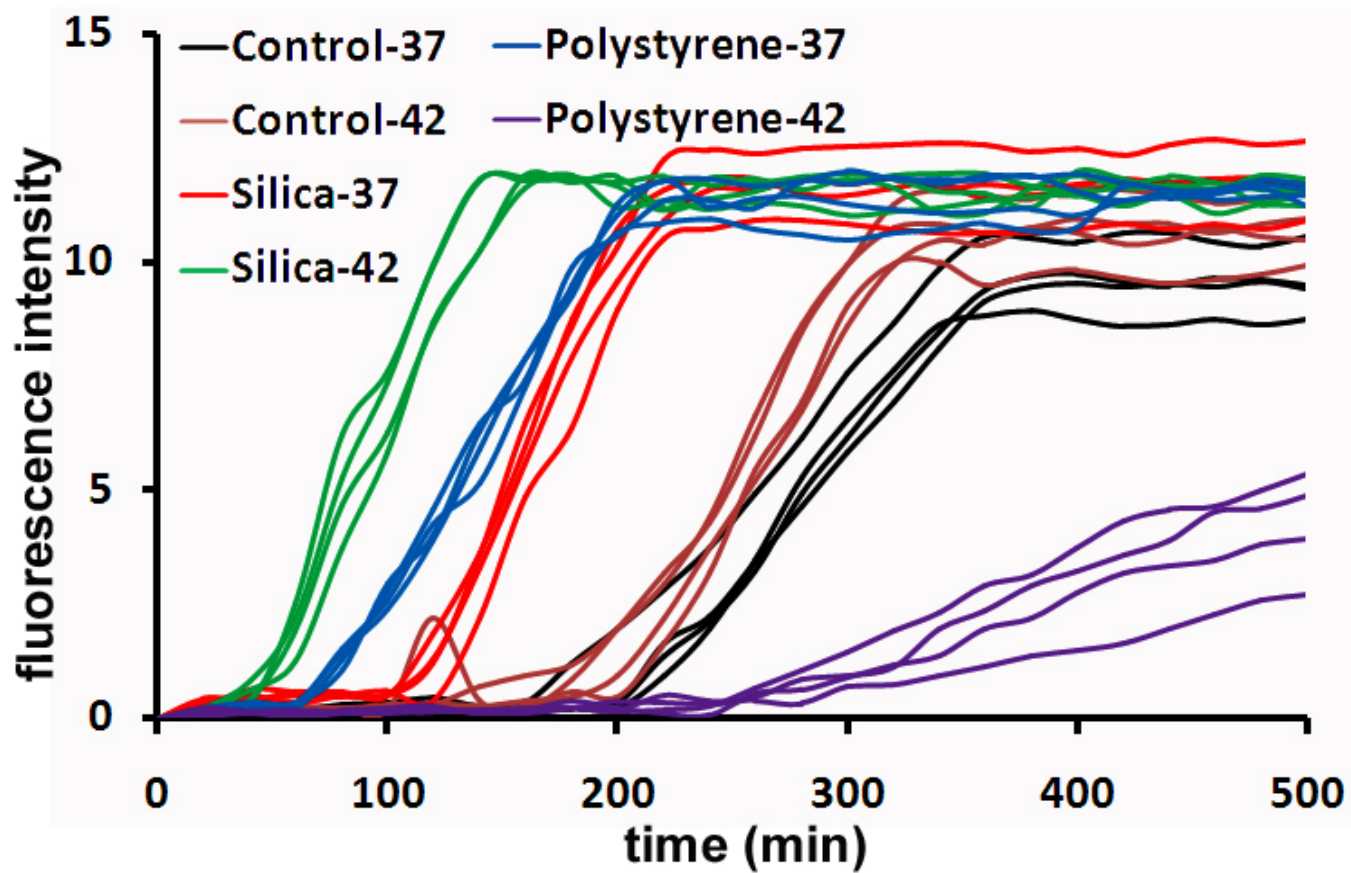


Figure 2

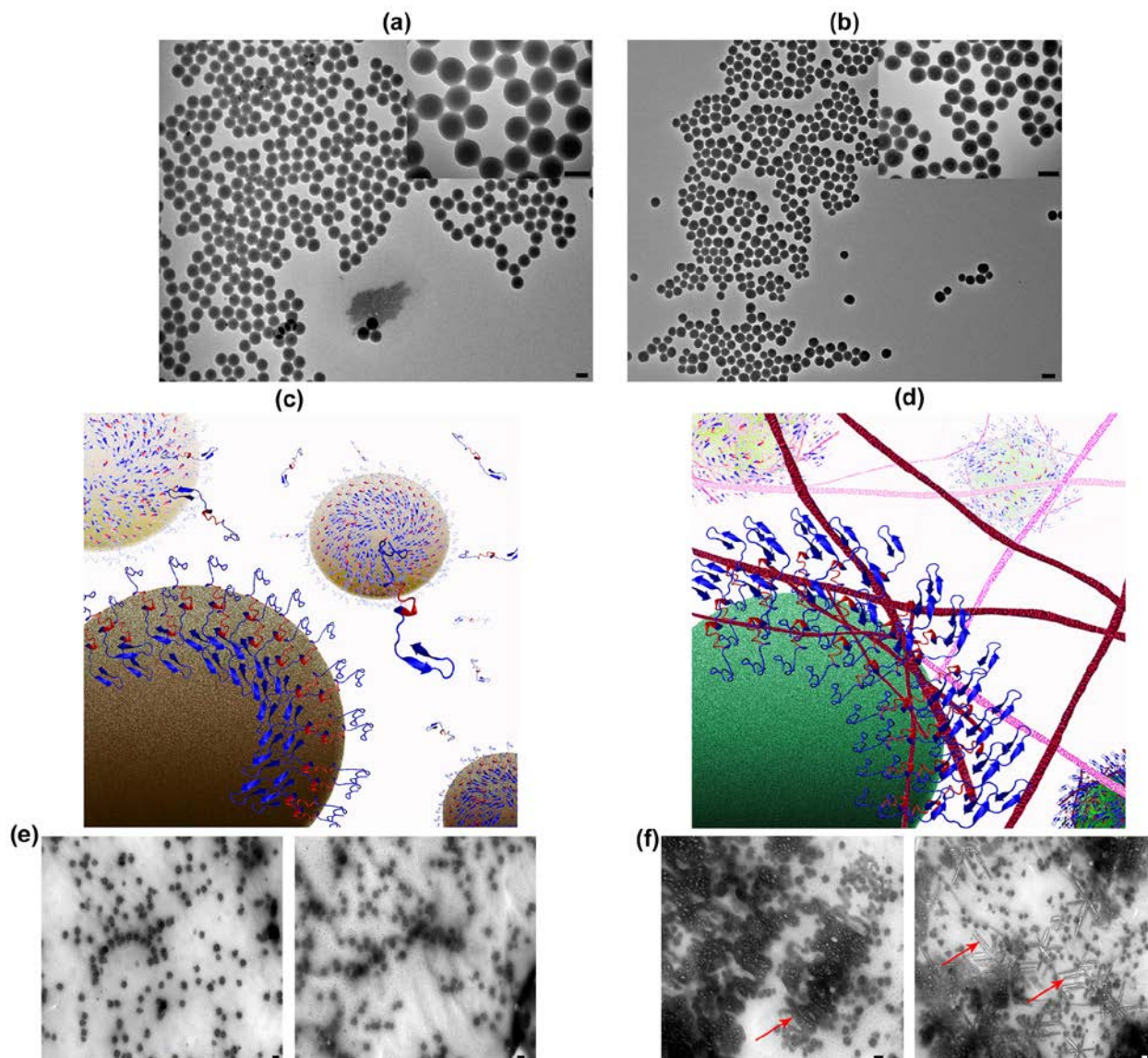
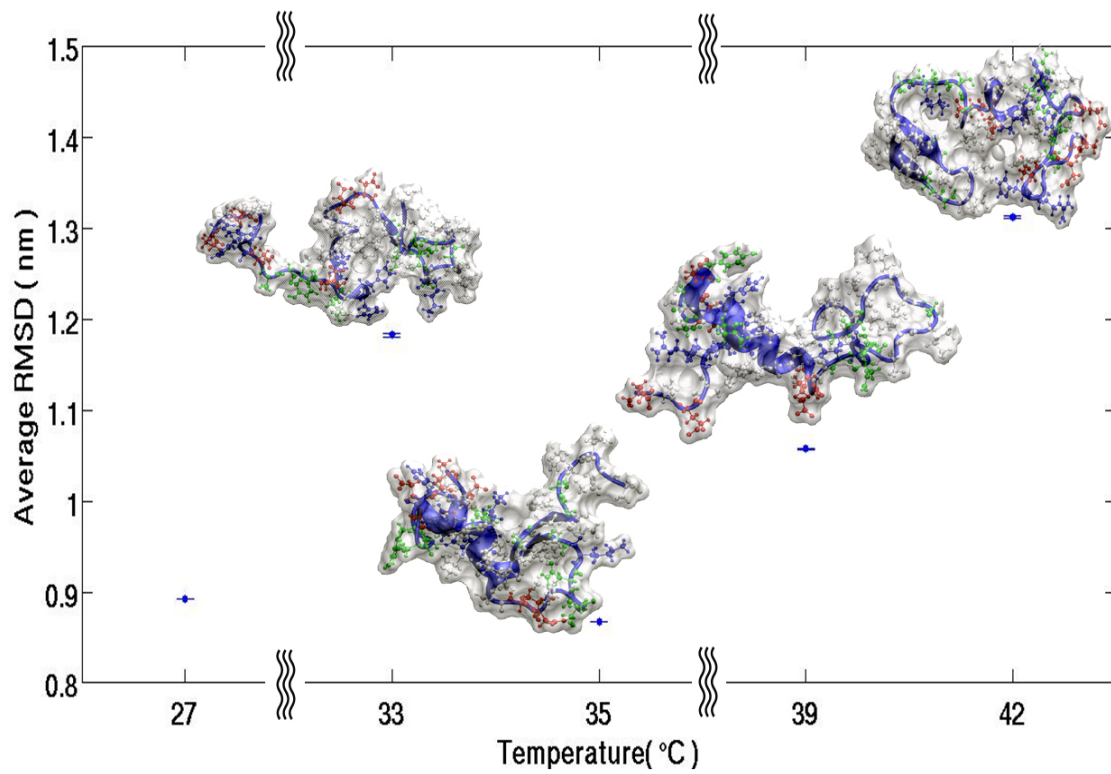
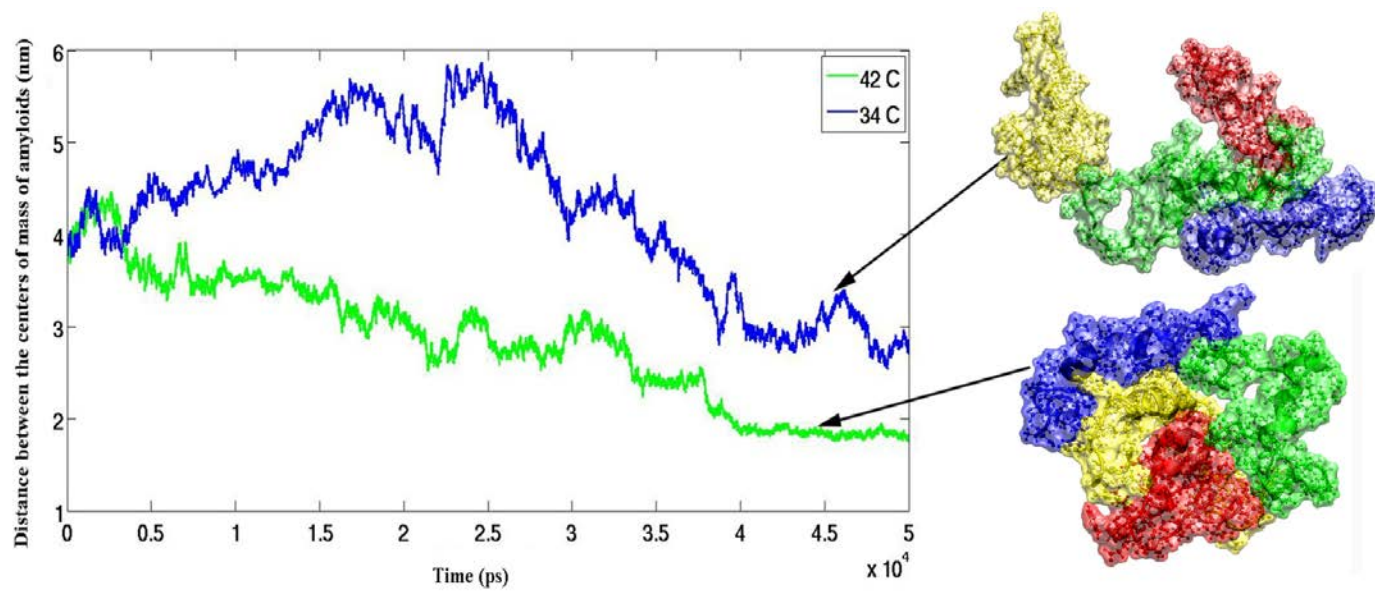


Figure 3



(a)



(b)

**Figure 4**

## Supporting information

# Physiological Temperature Has Crucial Role in Amyloid Beta in the Absence and Presence of Hydrophobic and Hydrophilic Nanoparticles

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- I) Experimental Section**
- II) Simulation Details**
- III) Simulation Results**

## I) Experimental Section

**Nanoparticles.** Carboxylated Polystyrene nanoparticles and silica nanoparticles with the mean size of 100 nm were purchased from invitrogen and Kisker-Biotech Inc, respectively.

**Monoclonal antibody.** Amyloid Beta ( $A\beta_{1-42}$ ) monoclonal antibody, 4G8, was purchased from Covance Inc.

HRP Labeled

**Amyloid Beta.**  $A\beta_{1-42}$  with sequence of MDAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA was used in this study.  $A\beta$  was synthesized by the W. M. Keck foundation, Biotechnology Resource Laboratory (Yale University), with an 80% purity (the remaining 20% of the lyophilized material is mainly water and some residual Trifluoroacetic acid).

$A\beta$  was dissolved in a 50:50 mixture of 1%  $NH_4OH$  and 100 mM Tris buffer followed by ultra-centrifugation (65 000 rpm; 1 000 000g) for 1 h at 4°C in a Beckman ultra-centrifuge in order to remove pre-existing amyloid fibrils, which are collected in the bottom of the vial; the upper 75% of the supernatant was carefully collected, and the concentration of  $A\beta$  was measured using the amount of absorbance at 275 nm according to the following equation:

$$C = A/\varepsilon \quad (1)$$

where C is the concentration in moles, A is the absorption (arbitrary units),  $\varepsilon$  is an extinction coefficient ( $M^{-1} cm^{-1}$ ). In order to make solutions with desired concentrations, the supernatant was diluted to 5  $\mu M$  using 13 mM sodium phosphate buffer, 0.02%  $NaN_3$ , pH 7.4. This solution was used immediately for experiments.

**Thioflavin T (ThT) assay.** In order to prevent the depletion of  $A\beta_{42}$  from solution by the adherence of  $A\beta_{42}$  to the plates' chamber walls, the plates were coated by poly-L-Lysine (PLL). Briefly, the PLL was diluted to 15  $\mu g/ml$  using Millipore ultra pure water. 300  $\mu l$  of this solution was aliquoted into each well and incubated at room temperature for 60 minutes. The wells were then aspirated completely and rinsed with 10 times their volume (3 ml) of Millipore ultra pure water. The plates were allowed to dry at room

temperature before use. 90  $\mu\text{l}$  of (10  $\mu\text{M}$  A $\beta$ 42 with 200  $\mu\text{M}$  ThT (from a 2mM stock solution in water)) per well was incubated in the absence or presence of 10  $\mu\text{l}$  of various nanomaterials, with different concentrations, per well at 37  $^{\circ}\text{C}$  and shaken at 700 rpm. Measurements were made at regular intervals (every 10 and 20 minutes, respectively) using a microplate reader with excitation and emission at 440 nm and 480 nm, respectively. Each experimental point is an average of the fluorescence signal of 8 wells (4 wells in each plate- we used 2 batches to be ensure that the data is reproducible) containing aliquots of the same solution (same particle and protein concentration). In order to be ensured about the suitability of ThT assay for various particles, the effects of ThT dye with various nanoparticles in the absence of A $\beta$ 42 were probed and the results confirmed that there is no considerable interaction with various particles and ThT dye.

The obtained kinetic data were analyzed assuming the typical sigmoidal behavior in order to extract the kinetic parameters of the bimodal fibrillation processes. An empirical sigmoidal equation was used:

$$y = y_0 + \frac{y_{max} - y_0}{1 + e^{-\frac{(t-t_{1/2})k}{2}}} \quad (1)$$

Where  $y$  is the fluorescence intensity at time  $t$ ,  $y_0$  and  $y_{max}$  are the initial and maximum fluorescence intensities, respectively,  $t_{1/2}$  is the time required to reach half the maximum intensity, and  $k$  is the apparent first-order aggregation constant. In addition, the lag time can be defined using the following equation:

$$\text{lagtime} = t_{1/2} - \frac{2}{k} \quad (2)$$

***Interactions of monoclonal antibody and A $\beta$  at various temperatures.*** A $\beta$  (1 ml at concentration of 5 $\mu\text{M}$ ) was incubated at various temperatures (32- 42 $^{\circ}\text{C}$ , with 1 $^{\circ}\text{C}$  intervals) for 30 min; then, monoclonal antibody (200 $\mu\text{L}$  with concentration of 1mg/ml) was added to the amyloid solution and incubated for additional 1 hour at the same temperature. The bound antibodies were detected by p-nitrophenyl

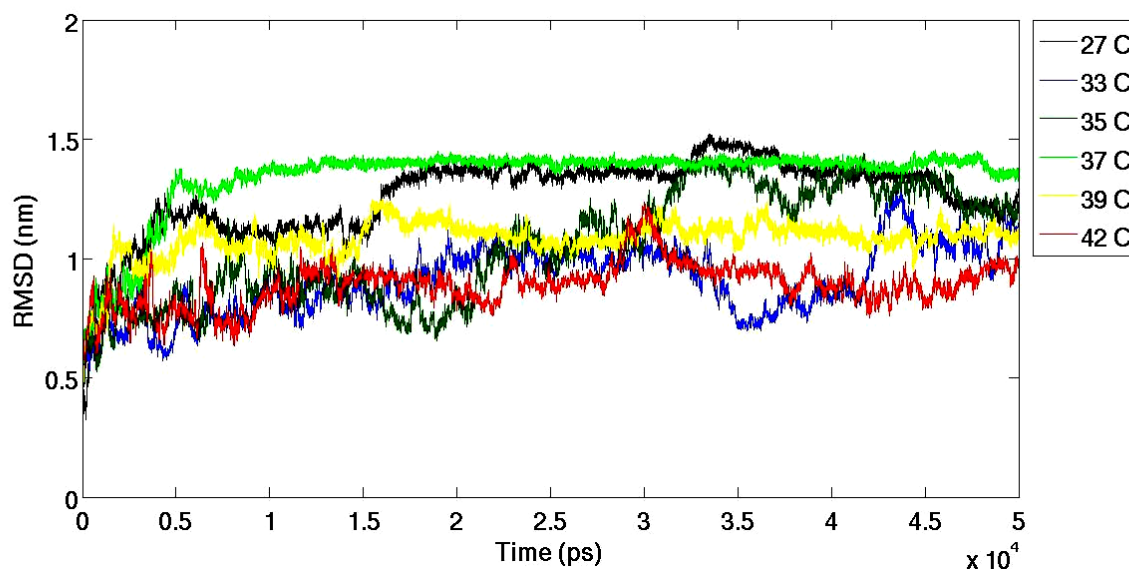
phosphate (Sigma) using the spectrophotometric plate reader (EON, BioTek Instruments, Inc; the absorbance was measured at 405 nm).

## II) Simulation details

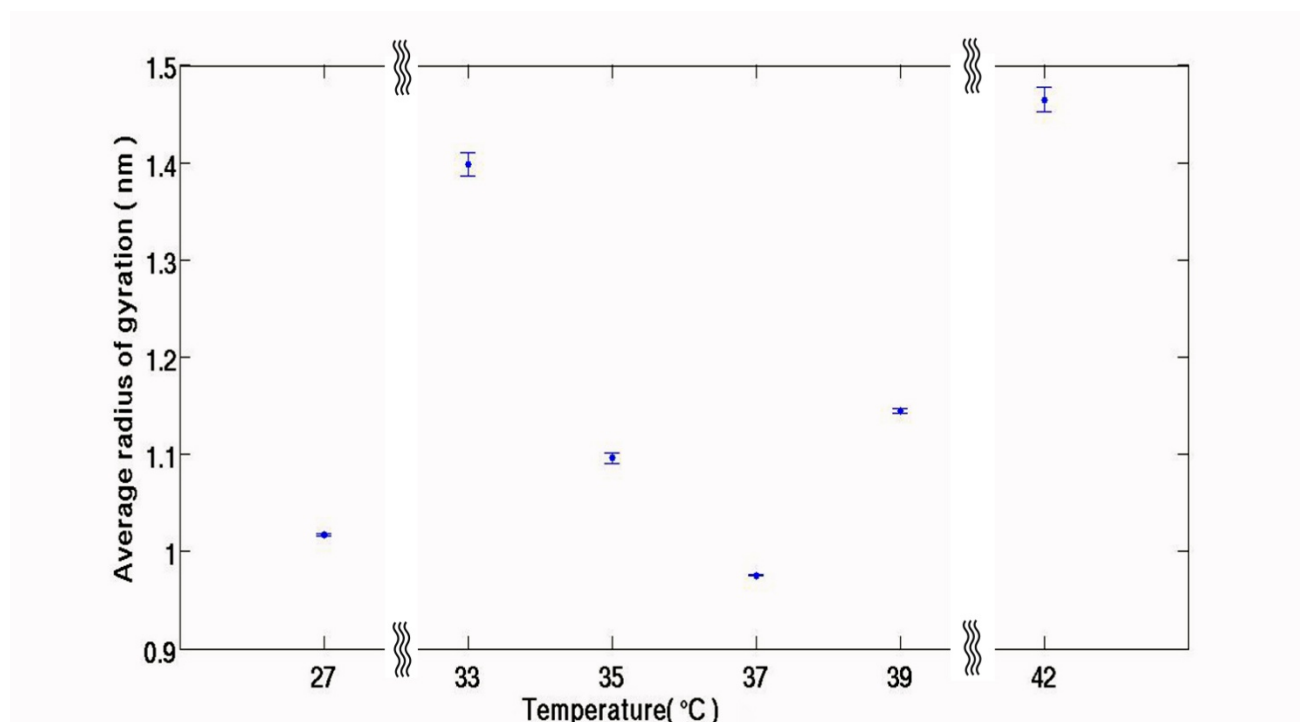
The GROMACS (version 4.5.3<sup>1</sup>) with OPLS\_AA force field<sup>2</sup> are employed for molecular dynamics simulations. Initial structure of amyloid is (Code: 1IYT) immersed in the center of a cubic box by condition that the walls are in a distance of 1.2 nm from the amyloid. The box contains about 15400 water molecules (i.e. SPC model) for simulation of an individual amyloid. To investigate dynamics of fibrillation we also simulate systems containing two or four amyloids. These systems are set in bigger boxes with about 22700 and 38300 water molecules, respectively. All the systems are neutralized by appropriate number of Na counter-ions. The system is minimized by using steepest descent algorithm and is equilibrated during 0.5 ns. Simulations are performed in NVT ensemble in constant temperatures between 27°C and 42°C (or 27°C, 33°C, 35°C, 37°C, 39°C, and 42°C) using Berendsen thermostat<sup>3</sup>. All bonds are constrained by LINCS algorithm<sup>4</sup> and the columbic interaction are treated by particle mesh Ewald method<sup>5</sup> in our periodic boundary condition. The length of each trajectory is 50 ns and time step is 2 fs. Snapshots were taken every 2 ps.

### III) Simulation Results

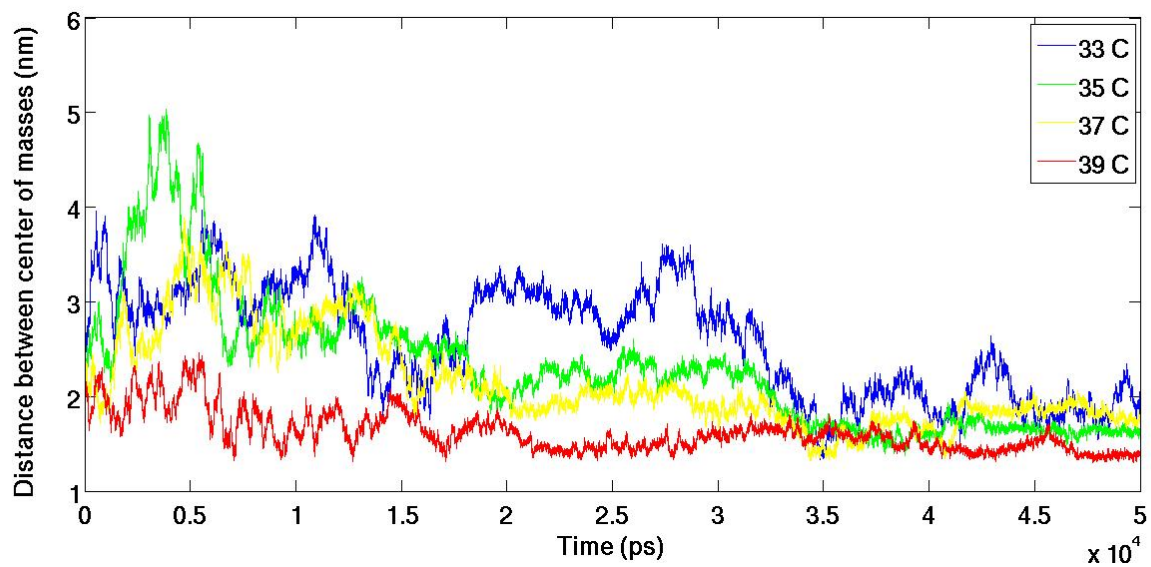
**RMSD & radius of gyration.** The same feature is seen on the simulations of four molecules in different temperatures of 34<sup>0</sup>C and 42<sup>0</sup>C (fig S5). Then the results of the simulation support experimental data and shows that fibrillation is temperature dependent and the effect is stronger on higher temperatures.



**Figure S1.** RMSD of amyloid structure from initial configuration (PDB) during the simulations in different temperatures.



**Figure S2.** Average radius of gyration of Amyloids in different temperatures.



**Figure S3.** Distance between the centers of mass of two amyloids as a function of time during simulations in different temperatures.

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