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Natural Seminal Amyloids as Targets for Development of Synthetic Inhibitors of HIV Transmission

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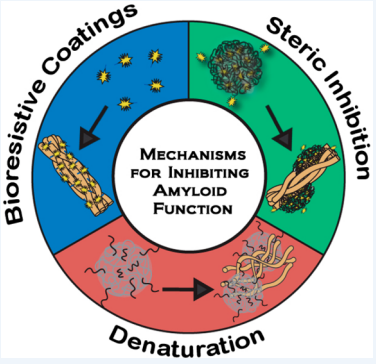
CONSPECTUS: Amyloids refer to a class of protein or peptide aggregates that are heterogeneous in size, morphology, and composition, and are implicated to play a central role in many neurodegenerative and systemic diseases. The strong correlation between biological activity and extent of aggregation of amyloidogenic proteins and peptides has led to an explosion of research efforts to target these materials with synthetic molecules or engineered antibodies to try to attenuate their function in disease pathology.



Although many of these efforts to attenuate amyloid function have shown great promise in laboratory settings, the vast majority of work has been focused on targeting amyloids associated with neurologic diseases, which has been met with significant additional challenges that preclude clinical evaluation. Only recently have researchers started applying their efforts toward neutralizing the activity of amyloids associated with non-neurologic diseases. For instance, small peptides present in high abundance in human semen have been found to aggregate into amyloid-like fibrils, with in vitro experiments indicating that these amyloid fibrils could potentially increase the rate of infection of pathogens such as HIV by over 400 000-fold during sexual contact.

Mechanistic investigations of naturally occurring seminal amyloid species such as Semen-derived Enhancer of Virus Infection (SEVI) and related natural peptide aggregates suggest that these materials interact strongly with virus particles and cell surfaces, facilitating viral attachment and internalization into cells and, thus, possibly promoting sexual transmission of disease. Such amyloid mediators in HIV transmission represent an attractive target for development of chemical approaches to attenuate their biological activity. For instance, the activity of seminal amyloids in genital fluids potentially allows for topical delivery of amyloid-targeting molecules, which could minimize common problems with systemic toxicity or permeability across biological barriers. In addition, molecules that target these amyloid mediators in viral attachment could potentially work synergistically with current antiviral agents to reduce the rate of HIV transmission.

This Account will briefly summarize some of the key evidence in support of the capability of SEVI to enhance viral infection, and will highlight examples, many from our group, of recent efforts aimed at inhibiting its activity using synthetic small molecules, oligomeric peptides, and polymeric materials. We present various chemical strategies that have shown promise for neutralizing the role of SEVI in HIV transmission including the development of aggregation inhibitors of SEVI fibril formation, small molecule amyloid binders that modulate the charge or structure of SEVI, and synthetic molecules that form bioresistive coatings on SEVI and inhibit its interaction with the virus or cell surface. We discuss some unique challenges that hamper translation of these molecular strategies toward clinical evaluation, and propose several opportunities for researchers to address these challenges.

INTRODUCTION

Sexually transmitted diseases (STDs) such as HIV affect millions of people, creating an unnecessary health and financial burden. The World Health Organization, for instance, estimates that almost 37 million people worldwide are infected with HIV, with an estimated 2 million new cases of HIV globally in 2014. The high cost of treatment and the widespread nature of STDs have prompted many research efforts focused on inhibiting transmission.

The most common and effective mechanism used to inhibit the spread of STDs is physical barriers such as condoms.[1,2] Despite the effectiveness of condom use in preventing STDs in a laboratory setting, the effectiveness of condoms globally, in real world settings, has reached a plateau due to errors during use as well as difficulties enforcing recurrent usage.[2−4] Because of these issues, alternative methods to prevent STDs are still necessary to further reduce the occurrence of STDs, with a large specific focus on the prevention of HIV transmission. The increased proportion of the global population that is HIV-negative but is at high risk of contracting HIV has led to efforts toward limiting the potential for HIV transmission prior to exposure.[5] Pre-exposure prophylaxis (PrEP) is a method aimed at inhibiting the spread of HIV through pre-emptive treatment

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with antiviral medications prior to exposure to infected individuals.[6] However, there are a host of natural factors that counteract these modes of protection against STDs.

One potentially important natural factor that is thought to play a significant role in HIV transmission is Semen-derived Enhancer of Virus Infection, or SEVI.[7,8] This naturally occurring amyloid material found in high abundance in semen has been reported to be responsible for an increase in the rate of infection of HIV by up to 400 000-fold (estimated from in vitro data).[7,9] Due to the increased risk of HIV transmission in the presence of SEVI, many research efforts are now focused on SEVI and mechanisms by which interactions between SEVI and HIV can be inhibited. This Account will summarize the prevailing hypothesis on the mechanism of SEVI-related disease transmission and will highlight some recent advances in potential treatment strategies to inhibit SEVI-mediated HIV infection.

NATURAL, PROTEIN-DERIVED FACTORS THAT AFFECT HIV TRANSMISSION

HIV is most commonly spread through sexual contact during intercourse, and the risk of infection is dependent on many factors.[4,10,11] For example, peptide aggregates present in semen have been shown to increase the infectivity of HIV. These amyloid aggregates are derived from one of several distinct peptide sequences, which arise as natural degradation products from proteins such as prostatic acid phosphatase (PAP) or from the naturally occurring semenogelin (SEM) proteins.[12−14]

The amyloidogenic peptide fragment ($PAP_{248–286}$) derived from PAP, for instance, has been shown to aggregate into amyloid-like fibrils called Semen-derived Enhancer of Virus Infection (SEVI, Figure 1A).[7] In the initial report of SEVI-mediated HIV infection, Münch and co-workers revealed evidence that SEVI efficiently binds HIV virions and facilitates virus transmission. Fluorescence labeling studies support direct binding interactions between SEVI and HIV (Figure 1B), as well as the potential for SEVI to facilitate internalization of HIV into target cells.[7,9] Flow cytometry studies conducted in our own lab have also shown that SEVI fibrils efficiently bound to target cells and promoted viral attachment.[15] Although SEVI fibrils have been implicated as a major factor responsible for increases in the rate of HIV transmission (Figure 1C and D), other natural factors present in semen may also contribute to the observed increase in the rate of HIV infection.[12,16] SEVI, however, is, to date, the most well-characterized and widely studied amyloid found in semen. Studies have shown that nonaggregated forms of $PAP_{248–286}$ (the major component of SEVI) do not enhance the infectivity of HIV, making the aggregated forms of this peptide the main target for designing effective inhibitors of seminal amyloid-mediated HIV infection.[7]

It is important to note that there is debate about the extent of the role that SEVI plays in the transmission of HIV.[17,18] A recent study suggests that preformed SEVI fibrils lack the ability to significantly penetrate vaginal mucosa and facilitate transport of bound HIV virions to the cervical matrix.[19] However, differences in structural features of SEVI were shown to be dependent upon the microenvironment, with little information on the impact of these structural differences on SEVI-mediated HIV infection. The lack of reliable animal models also hampers understanding of the role of SEVI on HIV infection in vivo. Additionally, both SEVI and SEM amyloids have been implicated as mediators of viral transmission, but their relative contribution in HIV infection remains unclear.

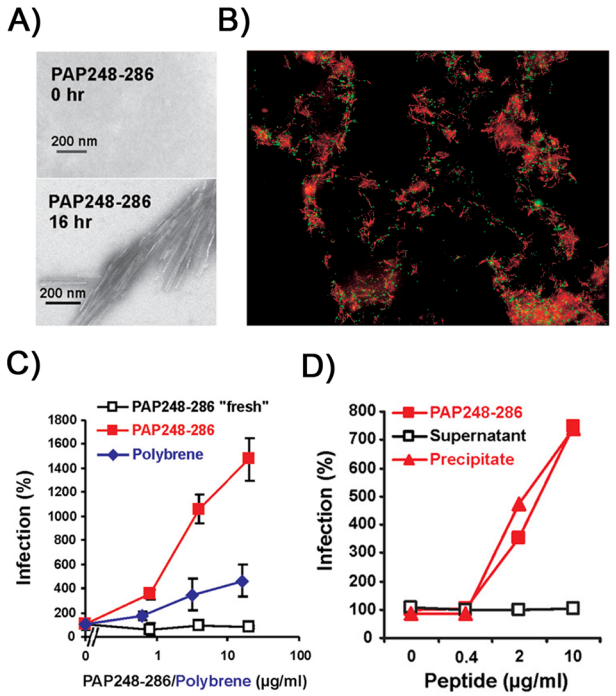

Figure 1. In vitro effects of SEVI on HIV infection. (A) Electron microscopy (EM) images of SEVI peptides after incubation for 0 or 16 h. (B) Fluorescence image showing the overlay of FITC-conjugated SEVI fibrils (false colored in red) and CFP-labeled HIV virus particles (false colored in green). (C) Results of HIV infection assays in the presence of either freshly diluted or overnight incubated SEVI or Polybrene, a cationic polymer known to improve retroviral gene transfer. (D) Results of HIV infection assays with SEVI. After a sample of the aggregated $PAP_{248–286}$ was removed, the suspension was centrifuged to isolate the supernatant and pellet prior to analysis in infectivity assays. These results show higher-order SEVI aggregates, and not monomers, are responsible for the enhancement of HIV infection. Adapted with permission from refs 7 and 9. Copyright 2007 Cell Press. Copyright 2009 American Society for Microbiology.

Since SEVI has also been implicated to facilitate clearance of microorganisms[8] and defective sperm[20] from the vaginal tract, it is unknown whether efforts to target SEVI in HIV transmission will adversely affect other potentially beneficial functions of this amyloid. However, validation of these other natural roles of SEVI are ongoing and, thus, we will restrict this account toward discussions of efforts aimed at neutralizing the role of SEVI in HIV infection using synthetic materials.

METHODS TO INHIBIT SEVI-MEDIATED HIV INFECTION

Small Molecule Inhibitors of SEVI-Mediated HIV Infection

Small molecules that can inhibit SEVI-mediated HIV infection have been developed with at least four distinct mechanistic hypotheses: (1) aggregation inhibitors of SEVI fibril formation, (2) modulators of the surface charge of SEVI, (3) generators of bioresistive coatings on SEVI fibrils, and (4) structural remodelers of preformed SEVI fibrils.

Amyloid fibrillization inhibitors are small molecules and metal ions that have been shown to prevent the aggregation of amyloidogenic peptides into higher order structures.[21−23] This approach has been used most extensively by chemists seeking

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to inhibit the aggregation of β-amyloid peptides in Alzheimer's disease, although a growing number of reports show success in designing inhibitors of SEVI fibril formation.[24,25] One example of a fibrillization inhibitor that has been studied for SEVI is epigallocatechin gallate (EGCG, Figure 2A).[21,23,26,27] EGCG

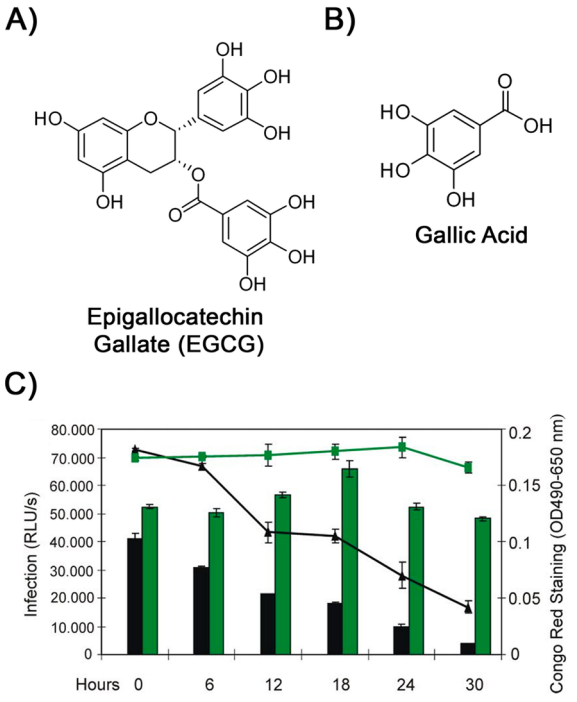

Figure 2. Effects of polyphenol compounds on fibril formation of SEVI peptides. (A) Structure of epigallocatechin (EGCG). (B) Structure of gallic acid. (C) Graph of SEVI-mediated HIV infection after incubation of SEVI with either EGCG (black) or gallocatechin (GC, green) for the given time period. Gallocatechin is a derivative of EGCG that has undergone hydrolysis of the ester, leaving the core catechin intact. The line graph represents the Congo red staining (a standard measure of amyloid content) of each SEVI sample prior to the analysis of HIV infection indicated by the bar graph. These results show that decreasing SEVI fibril content is directly related to decreasing enhancement of HIV infection. Adapted with permission from ref 23. Copyright 2009 National Academy of Sciences.

has been suggested to bind to a pocket of several hydrophilic amino acid residues within the peptide ($PAP_{248-286}$) that makes up SEVI.[21] This binding event putatively leads to a sequestration of monomeric peptide, and, thus, inhibits aggregation of $PAP_{248-286}$ into mature SEVI fibrils (Figure 2C).[23]

Interestingly, a recent study has found that a segment of EGCG, gallic acid (Figure 2B), is a potent binder of SEVI fibrils and purportedly inhibits SEVI-mediated interactions with HIV and target cell surfaces by decreasing the positive charge potential on the surface of mature SEVI amyloids.[27] The small molecule surfen is another example of a SEVI-binding molecule that inhibits the interaction between SEVI and cellular and viral surfaces.[28]

Prior to reports on the effects of EGCG and its derivatives as aggregation inhibitors of SEVI, we reported an initial study of a hexa(ethylene glycol) derivative of benzothiazole aniline (BTA-EG_6, Figure 3B) as a small molecule inhibitor of SEVI-mediated HIV infection.[15] The amyloid-binding core of this molecule shares many structural similarities with Pittsburgh compound B

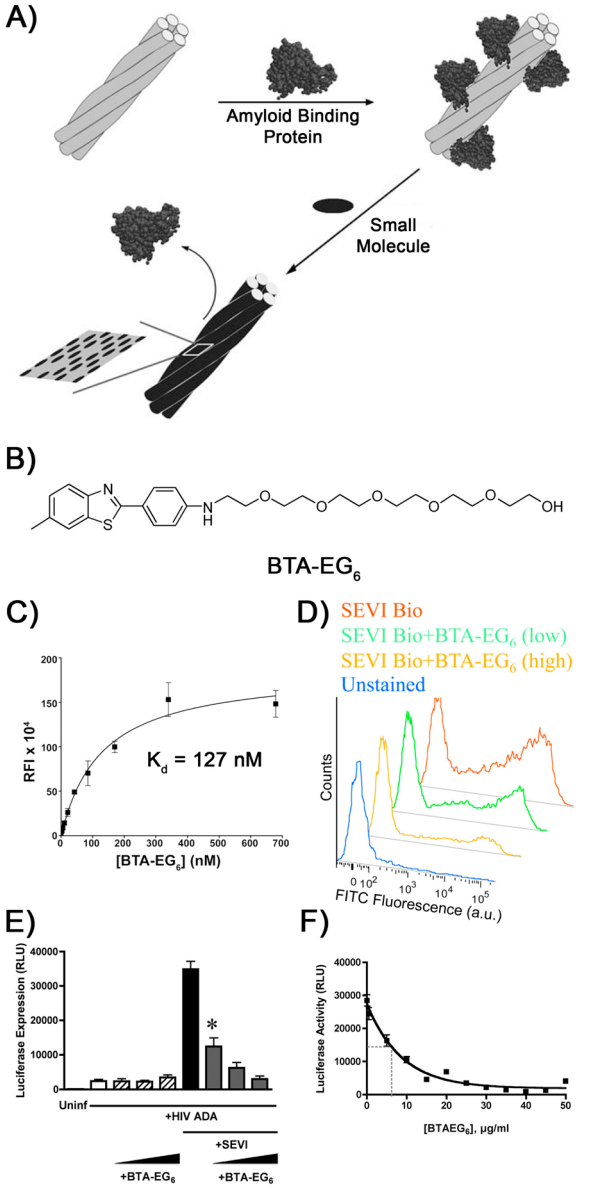

Figure 3. Effects of BTA-EG_6 on SEVI mediated HIV infection. (A) Cartoon showing the inhibition of protein−amyloid interactions by formation of bioresistive coatings after binding of small molecules to an amyloid fibril. (B) Structure of BTA-EG_6. (C) Binding curve for BTA-EG_6 to SEVI fibrils giving an estimated K_d of 127 nM. (D) Flow cytometry analysis of a SEVI-biotin (SEVI Bio) conjugate bound to cell surfaces in the presence or absence of BTA-EG_6 showing that BTA-EG_6 can inhibit SEVI-membrane interactions. SEVI was detected with a streptavidin-FITC conjugate. (E) Results of HIV infection assay in the presence of SEVI and BTA-EG_6. (F) Dose−response curve of HIV infection results derived from (E) that provides an estimate of IC_{50} against SEVI-mediated HIV infection of 6.6 μg/mL (13 μM). Adapted with permission from refs 15 and 30. Copyright 2010 American Society for Biochemistry and Molecular Biology. Copyright 2006 Wiley-VCH.

(PiB),[29] which has been shown to have excellent specificity for targeting amyloids in vivo. BTA-EG_6 was not only a potent binder of SEVI fibrils (K_d = 127 nM, Figure 3C), but it was also able to inhibit SEVI binding interactions with Jurkat and cervical cells (Figure 3D). We proposed that BTA-EG_6 binds with high density and uniformity to SEVI creating a bioresistive coating (Figure 3A),[30,31] inhibiting SEVI interactions with HIV

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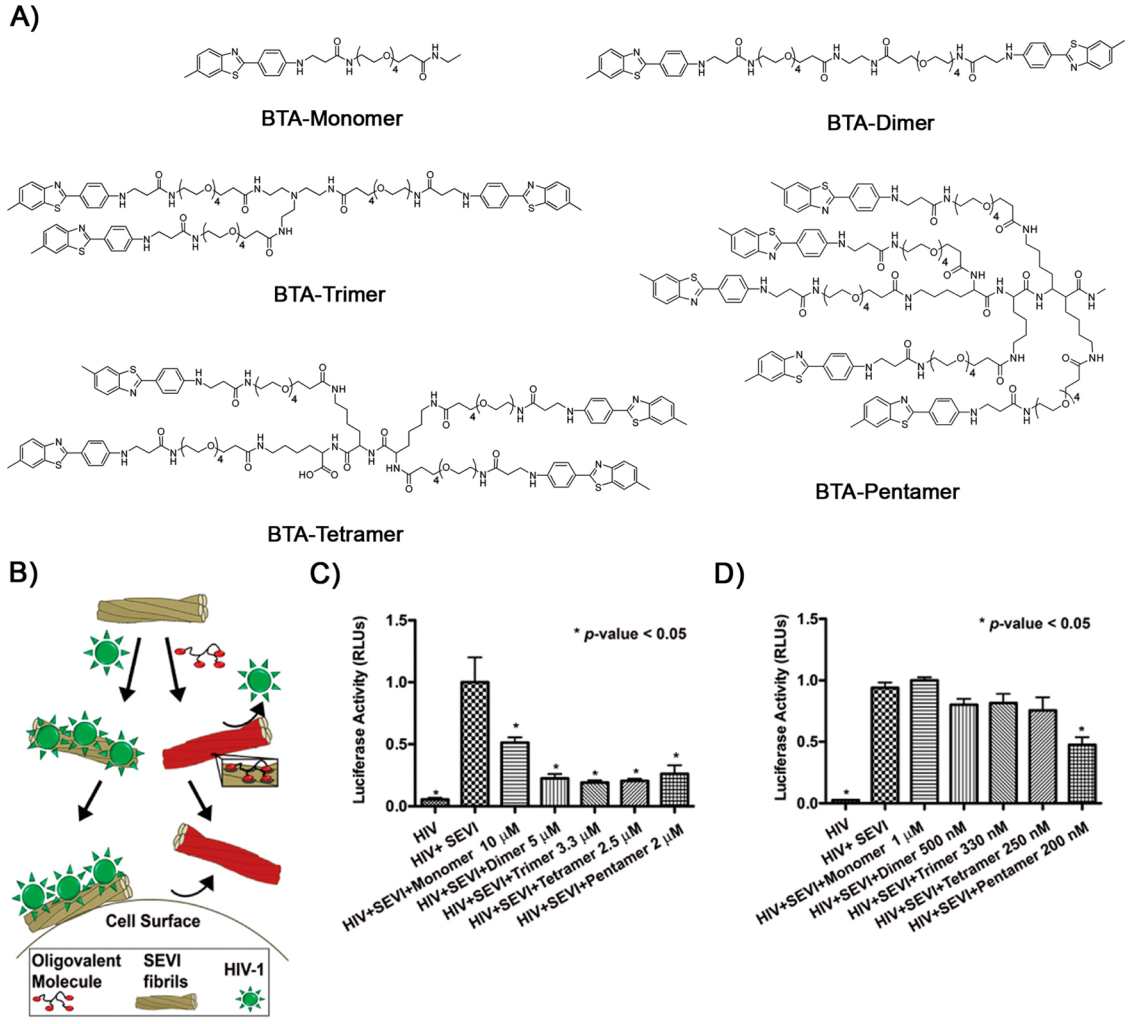

Figure 4. Oligomeric amyloid-targeting analogues of benzothiazole aniline (BTA) inhibit SEVI-mediated HIV infection. (A) Structures of monomeric and oligomeric BTA conjugates. (B) Cartoon showing the potential of BTA oligomers to coat the surface of SEVI fibrils and inhibit SEVI−HIV interactions and further inhibit SEVI-mediated viral attachment to cells. (C) Results of HIV infection assays in the presence of SEVI and oligomeric BTA molecules carrying one to five BTA moieties. (D) Results from HIV infection assays using the same BTA molecules in (C), with the concentrations of molecules normalized to 1 μM total BTA. Adapted with permission from ref 36. Copyright 2012 American Chemical Society.

and cell surface proteins and reducing SEVI-mediated HIV transmission (Figure 3E). This reduction in SEVI-enhanced HIV infection was dose-dependent, with an IC_{50} against SEVI-mediated HIV infection of 13 μM (Figure 3F). Further evidence showed that BTA-EG_6 inhibits semen-mediated HIV infection, presumably as a result of BTA-EG_6 binding to the naturally occurring SEVI present in the pooled semen sample.[15] Finally, BTA-EG_6 was found to be minimally toxic to cervical cells at concentrations that were found to be effective against SEVI-enhanced HIV infection. Importantly, BTA-EG_6 did not elicit a proinflammatory response, which is a problem often found in previous microbicide candidates.[32,33] Taken together, these results suggest that BTA-EG_6 represents a promising novel molecule for neutralizing the effects of SEVI on HIV infection.

Lastly, a recent study has identified a small molecule, CLR01, that could interact with lysine and arginine amino acid residues on SEVI,[34] leading to inhibition of the formation of seminal amyloid fibrils and structural remodelling of existing fibrils.[35] CLR01 was also able to inhibit interactions between SEVI and HIV virions.

Oligomeric and Polymeric Inhibitors of SEVI-Mediated HIV Infection

Building on the successful results of using BTA-EG_6 to reduce SEVI-mediated HIV infection, we explored two approaches to increase potency for neutralizing the effects of SEVI-enhanced HIV transmission: (1) development of a series of oligomeric analogues of amyloid-binding BTA groups to study the dependence of binding and activity of synthetic compounds as a function of valence number, and (2) development of BTA-containing polymeric nanoparticles to examine whether steric bulk could play a role in inhibiting the effects of SEVI on HIV infection.[36,37]

A key feature of amyloid aggregates is that they are made up of many identical proteins or peptides that putatively present multiple identical sites along their surface for the binding of small molecules.[38,39] Under such circumstances, a potentially useful approach to improve the binding affinity to an amyloid target is to design molecules that can engage in multiple, simultaneous binding events (i.e., multivalent binding) to multiple binding sites that are in close proximity to each other. Accordingly, we previously reported several oligomeric analogues of BTA, incorporating one to five BTA moieties

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per molecule (Figure 4A). We hypothesized that addition of each successive BTA moiety would show improved binding affinity to SEVI, which we presumed would correlate with improved inhibition of SEVI-mediated HIV infection (Figure 4B).[36]

We indeed found a general trend of improved binding affinity as a function of valence number for these oligomeric BTA compounds. In the most extreme comparison, we found that a pentameric BTA molecule (Figure 4A) had an apparent binding affinity of 400 pM to SEVI, while the monomeric BTA compound had a 590-fold higher K_d of 236 nM. This improved binding affinity of the BTA-pentamer correlated with an IC_{50} for inhibiting SEVI-mediated HIV infection of 200 nM (Figure 4C and D), which was 65-fold more potent than parent monomeric BTA-EG_6 (IC_{50} of 13 μM). This work demonstrates the use of multivalency as a design principle for the development of synthetic amyloid-targeting materials, specifically with improved efficacy against SEVI-enhanced HIV infection over the monovalent parent molecule, BTA-EG_6.

While these prior studies on multivalent amyloid-targeting compounds showed promise for designing potent neutralizers of SEVI activity, the improved effects on SEVI-enhanced HIV infection by the BTA oligomers was modest compared to the effects of multivalency on apparent binding affinity. This observation led to the hypothesis that perhaps the increased size of the oligomeric compounds versus monomeric BTA could potentially play a dominant role over improved binding affinity for inhibiting the interaction of SEVI with HIV. To test this hypothesis, we prepared an acrylate-based polymer containing ~200 BTA-EG_6 moieties per polymer chain, which could readily be formulated into nanoparticles with average diameter of ~200 nm (Figure 5A).[37] Transmission electron microscopy (TEM) analysis supported that these nanoparticles bound to SEVI fibrils, potentially generating a "crust" of nanoparticles on the SEVI surface (Figure 5B). Examination of the apparent binding affinity of the free polymeric material revealed a K_d of 206 nM to SEVI fibrils, which was similar to the measured K_d of monomeric BTA-EG_6 to SEVI (Figure 3C). We attribute the lower than expected binding affinity of the BTA-containing polymer (which presumably is capable of multivalent binding) to the potential for the BTA moieties to hide within the hydrophobic core of the polymer while in aqueous solution, rendering a significant fraction of the amyloid binding groups unavailable for binding to SEVI. Interestingly, however, we found that this polymer exhibited potent activity for reducing SEVI-mediated HIV infection with an IC_{50} of 210 nM, which is comparable to the activity of a pentameric BTA molecule (Figure 4A) for inhibiting SEVI-enhanced infection of HIV. Furthermore, these amyloid-binding polymers exhibited a ratio of K_d:IC_{50} of ~1:1, suggesting that the majority of polymer chains bound to SEVI contribute to inhibition of SEVI activity. This result was in contrast to the disproportionate K_d:IC_{50} ratios for the monomeric (~1:100) and pentameric BTA (1:500) compounds, which suggested that relatively few of these non-polymeric compounds bound to SEVI contribute to neutralization of SEVI in HIV infection. These results are consistent with the hypothesis that steric bulk from amyloid targeting materials improves their ability to inhibit SEVI–HIV interactions. Another possible explanation for these results is that the BTA monomers, oligomers, and polymers could disproportionately interact with off target species within the media during the infectivity assays and affect estimates of K_d:IC_{50} ratios. The

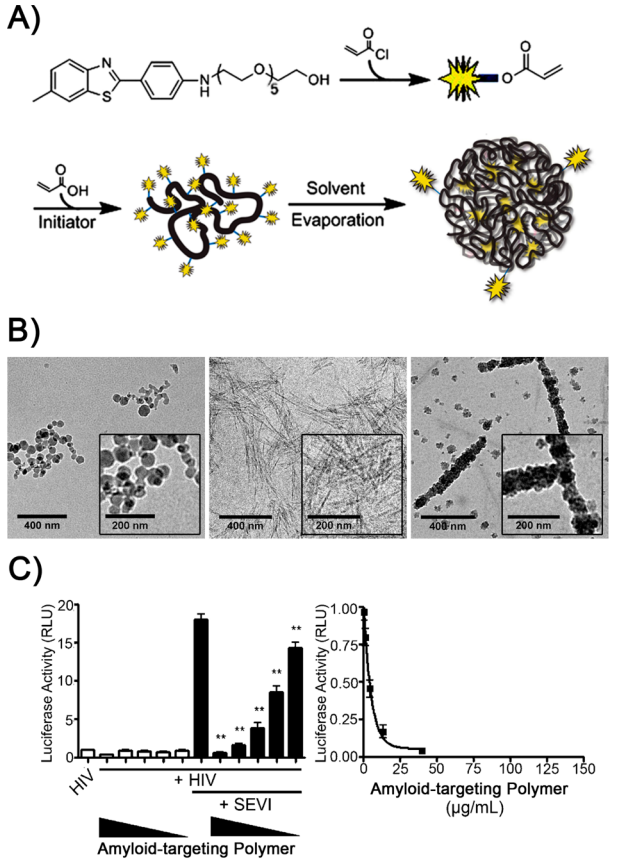

Figure 5. Amyloid-binding nanoparticles inhibit SEVI-mediated HIV infection. (A) General synthetic strategy for preparation of amyloid binding polymeric nanoparticles. (B) EM images of amyloid-binding nanoparticles (left) and SEVI fibrils alone (middle) or after incubation together (right). (C) Graph and dose–response curve for SEVI-mediated HIV infection assays in the presence of amyloid-targeting nanoparticles. Adapted with permission from ref 37. Copyright 2015 American Chemical Society.

polymeric nanoparticles used in these studies exhibited an IC_{50} value of 59 nM (based on polymer concentration) for inhibiting SEVI-mediated HIV infection (Figure 5C), which represents the most potent SEVI-neutralizing compound reported to date.

Polymeric materials that do not contain amyloid-targeting groups have also been examined for their capability to reduce SEVI-mediated HIV infection.[9,16] Polyanionic materials such as heparin sulfate, for instance, have strong electrostatic interactions with cationic SEVI amyloids, and showed promise for inhibiting SEVI-mediated HIV infection in vitro. In clinical trials, however, several polyanionic materials were ineffective in the prevention of HIV transmission, possibly due to their general proinflammatory properties that lead to increased viral transmission.[9,40−42]

Finally, we recently demonstrated that hydrophobic polymeric nanoparticles that lacked an amyloid-targeting group could also inhibit SEVI-mediated HIV infection (Figure 6).[43] These polymeric nanoparticles were nontoxic (Figure 6B) and were shown to reduce the β-sheet content of preformed SEVI fibrils by up to 45% (Figure 6A), which was accompanied by a 60% reduction of SEVI-mediated HIV infection (Figure 6C). Hydrophilic polymers, on the other hand, did not affect SEVI-mediated HIV infection, suggesting that affecting the β-sheet

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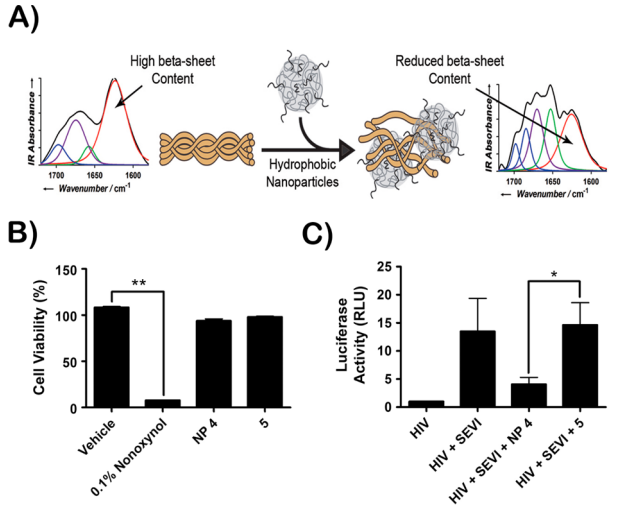

Figure 6. Hydrophobic nanoparticles disrupt the β-sheet content of SEVI amyloid fibrils and inhibit SEVI-mediated HIV infection. (A) Cartoon showing the disruption of β-sheet content of SEVI fibrils using hydrophobic nanoparticles. The graphs depict the IR spectroscopy measurements of the amide I region of preformed SEVI fibrils after incubation on a hydrophilic (left) or hydrophobic (right) surface for 6 h. The red curves indicate the relative abundance of β-sheet character in the fibrils. (B) Effects of polymeric hydrophobic nanoparticles (**NP 4**) or hydrophilic polymer (**5**) and nonoxynol-9 on cell viability. (C) Effects of **NP 4** and polymer **5** on SEVI-mediated HIV infection. Adapted with permission from ref 43. Copyright 2017 American Chemical Society.

content of SEVI with hydrophobic materials could be exploited in the design of SEVI neutralizing agents.

ANALYSIS OF APPROACHES TO INHIBIT SEVI-MEDIATED HIV INFECTION

While many molecular approaches to inhibit SEVI-mediated HIV infection have proven to be effective in cellular assays, it remains to be seen how effective these methods will be in a clinical setting. For instance, for fibrillization inhibitors to be effective in vivo, individuals would need to be treated with high doses of compounds prior to significant aggregation of seminal amyloidogenic peptides. Given that mature SEVI fibrils are already present in semen prior to introduction into the vaginal tract,[12,16] it is unlikely that inhibitors of fibrillization would be successful for inhibiting SEVI-mediated HIV infection. Alternatively, compounds that can disaggregate or remodel preformed fibrils could be more effective than aggregation inhibitors if they could rapidly disaggregate/remodel SEVI fibrils before they come in contact with HIV virions. To date, however, there are relatively few reports of molecules that can disaggregate SEVI fibrils,[44] even though many groups have reported small molecules that effectively disaggregated other types of amyloid fibrils.[45] This current void of known compounds that can rapidly disaggregate or remodel SEVI fibrils may, hence, represent an opportunity for chemists to develop a novel class of PrEP for SEVI-mediated HIV infection.

Amyloid-binding BTA monomers and oligomers have shown remarkable efficacy for reducing SEVI-mediated HIV infection.[15,36,37] The bioresistive coatings generated by these amyloid-binding materials provide a nontoxic barrier to SEVI–HIV interactions, and attenuate SEVI-mediated enhancement of HIV infection. These BTA monomers and oligomers are water-soluble and, therefore, are amenable to aqueous formulations for topical application. However, the difficulty of synthesis and isolation of oligomeric amyloid-binding materials, in particular, introduces a synthetic challenge for large-scale production.[36]

Amyloid-binding polymeric nanoparticles may provide a more practical approach for large-scale production of effective inhibitors of SEVI-mediated HIV infection.[37] BTA-carrying polymers were easily prepared through free-radical polymerization and were potent inhibitors of SEVI-mediated HIV infection. Controlled polymerization techniques[46,47] may offer opportunities to improve issues with reproducibility in polymer preparation. The use of nanoparticles as therapeutics is now a burgeoning field and has shown increased application in clinical trials.[48] Amyloid-binding polymeric nanoparticles should be amenable to formulation and application together with pre-existing contraceptives such as intrauterine devices (IUD) and intravaginal rings. The addition of combination anti-HIV treatments, including amyloid neutralizing agents, to such contraceptive devices may enable a novel prophylactic option to inhibit the spread of HIV.[49]

Polyanionic materials have progressed further in clinical evaluation than many other treatment options against HIV infection. However, natural polyanionic materials were not effective against HIV transmission, possibly due to an inflammatory response leading to increased viral loads.[16,32,42,50,51] One possible approach to circumvent the problem of inflammation by polyanionic materials could be to use hydrophobic materials, which we have demonstrated can reduce the β-sheet content of SEVI and neutralize its effect in HIV infection assays.[43]

CONCLUSIONS

This Account summarizes some current research efforts aimed at targeting SEVI with synthetic molecules and reducing its effect on HIV transmission. Thus far, SEVI-targeted agents have shown great promise for the development of molecular approaches to inhibit SEVI-enhanced HIV infection. Understanding the molecular details of the interaction of small molecules with SEVI remains an important challenge that could lead to the development of more effective SEVI-neutralizing agents.

For instance, the amyloid-binding BTA molecules summarized here target β-sheet rich structural features found in SEVI as well as in other amyloid aggregates. Structural targeting of amyloids is an active area of research. Antibodies that targeted structural features of SEVI (rather than an amino acid sequence specific to $PAP_{248-286}$), for example, have been used to detect SEVI in semen samples. While it is unclear whether these antibodies would survive the low pH of cervical mucus or the abrupt increase in pH upon introduction of seminal fluid during intercourse, studies have shown that antibodies can be found within cervicovaginal fluids, suggesting that antibodies raised against SEVI peptides may be rendered sufficiently stable.[52] Additionally, there is a potential opportunity for development of sequence specific small molecules that target SEVI peptides and circumvent potential issues of poor stability of proteins.

There is a large global demand for effective methods to prevent HIV transmission, and SEVI represents a viable target that is naturally abundant and easily detectable in semen for development of small molecule microbicide supplements.[16] As discussed throughout this Account, research into novel approaches for SEVI targeting can lead to promising candidates that reduce SEVI-mediated HIV infection, and more general-

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ized insights into the biological function(s) of amyloid fibrils. We hope that the research summarized herein will stimulate excitement from chemists with a broad spectrum of expertise, and will engage new research ideas aimed at seizing opportunities to eliminate the role of SEVI and related seminal protein aggregates in sexually transmitted diseases.

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Notes

The authors declare no competing financial interest.

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Stephen Dewhurst is Professor and Chair of Microbiology and Immunology, and Vice Dean for Research, at the University of Rochester School of Medicine and Dentistry. Prior to joining the faculty at UR, he was a postdoctoral fellow in the lab of Prof. Jim Mullins at the Harvard School of Public Health. He received his B.S. from Bristol University (England) and his Ph.D. in Pathology and Microbiology from the University of Nebraska Medical Center under the direction of Prof. David Volsky. His current research interests include exploring new therapeutic strategies for HIV-associated neurocognitive disorders, developing new vaccines for influenza and for HIV, and understanding the functional role of amyloid fibrils present in human semen.

Jerry Yang is an Associate Professor of Chemistry and Biochemistry at the University of California, San Diego. Prior to joining the faculty at UCSD in 2003, he was a postdoctoral fellow in the lab of Prof. George Whitesides at Harvard University. He received his B.S. from UC Berkeley and his Ph.D. in Chemistry from Columbia University under the direction of Prof. Ronald Breslow. His current research interests include exploring new diagnostic and therapeutic strategies for amyloid-associated diseases.

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