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Proteins behaving badly. Substoichiometric molecular control and amplification of the initiation and nature of amyloid fibril formation: lessons from and for blood clotting☆

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ABSTRACT

The chief and largely terminal element of normal blood clotting is considered to involve the polymerisation of the mainly α-helical fibrinogen to fibrin, with a binding mechanism involving 'knobs and holes' but with otherwise little change in protein secondary structure. We recognise, however, that extremely unusual mutations or mechanical stressing can cause fibrinogen to adopt a conformation containing extensive β-sheets. Similarly, prions can change morphology from a largely α-helical to largely β-sheet conformation, and the latter catalyses both the transition and the self-organising polymerisation of the β-sheet structures. Many other proteins can also do this, where it is known as amyloidogenesis. When fibrin is formed in samples from patients harbouring different diseases it can have widely varying diameters and morphologies. We here develop the idea, and summarise the evidence, that in many cases the anomalous fibrin fibre formation seen in such diseases actually amounts to amyloidogenesis. In particular, fibrin can interact with the amyloid-β (Aβ) protein that is misfolded in Alzheimer's disease. Seeing these unusual fibrin morphologies as true amyloids explains a great deal about fibrin(ogen) biology that was previously opaque, and provides novel strategies for treating such coagulopathies. The literature on blood clotting can usefully both inform and be informed by that on prions and on the many other widely recognised (β-)amyloid proteins. A preprint has been lodged in bioRxiv (Kell and Pretorius, 2016).

Contents

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"Novel but physiologically important factors that affect fibrinolysis have seldom been discovered and characterized in recent years" (Weisel, 2011)

1. Introduction: the thermodynamics of protein folding and prion proteins, and the existence of multiple macrostates

Starting with Anfinsen's famous protein re-folding experiments (Anfinsen, 1973; Anfinsen et al., 1961), showing that an unfolded protein would refold reliably to its commonest (and original) state as found in the cell, it was widely assumed that the normal macrostate of a folded protein was that of its lowest free energy.

If one allows each amino acid to have n distinct conformational substates, the total number n^m scales exponentially with the number m of amino acids (Kell, 2012), and until recently exhaustive calculations to determine whether the 'preferred' conformation was of lowest free energy were prohibitively expensive (Piana et al., 2014, 2012, 2013; Verma and Wenzel, 2009); indeed, they still are save for small proteins, so this question of whether the 'normal' conformation is that of lowest free energy (±kT) is certainly not settled in general terms, and (as we shall see in many cases) forms of lower free energy than the 'normal' one are in fact both common and of high biological significance.

In particular, as is again well known (Aguzzi and Calella, 2009; Caughey et al., 2009; Colby and Prusiner, 2011; Prusiner, 1998), and starting with Virchow's observations in 1854 (Sipe and Cohen, 2000), a number of proteins of a given sequence can exist in at least two (or more) highly distinct conformations (e.g. (Chiti and Dobson, 2006; Eisenberg and Jucker, 2012)). Typically the normal ('benign') form, as produced initially within the cell, will have a significant α-helical content and a very low amount of β-sheet, but the abnormal ('rogue') form, especially when in the form of an insoluble amyloid (Dobson, 2013), will have a massively increased amount of β-sheet (Baldwin et al., 1994; Groveman et al., 2014; Harrison et al., 1997; Jack et al., 2006; Jahn et al., 2008; Pan et al., 1993) (but cf (Ow and Dunstan, 2014)), whether parallel or antiparallel (Tycko and Wickner, 2013). The canonical example is the prion protein PrP^c, whose abnormal form is known as PrP^{Sc}, and whose PrP^c structure is shown in Fig 1. As is also well known, the monomers of the abnormal form may catalyse their own formation from the normal form, and will typically go on to self-assemble to form oligomers, protofibrils and finally insoluble fibrils (Colby and Prusiner, 2011). (A particular hallmark of PrP^{Sc}, and indeed a common basis for its assay, is its very great resistance to proteolysis relative to PrP^c, typically assessed using proteinase K (Basu et al., 2007; Grassi et al., 2000; Mishra et al., 2004; Saá and Cervenakova, 2015; Saleem et al., 2014; Saverioni et al., 2013; Silva et al., 2015)).

Fig. 1. PrP^c conformation of human prion protein (1HJM at PDB).

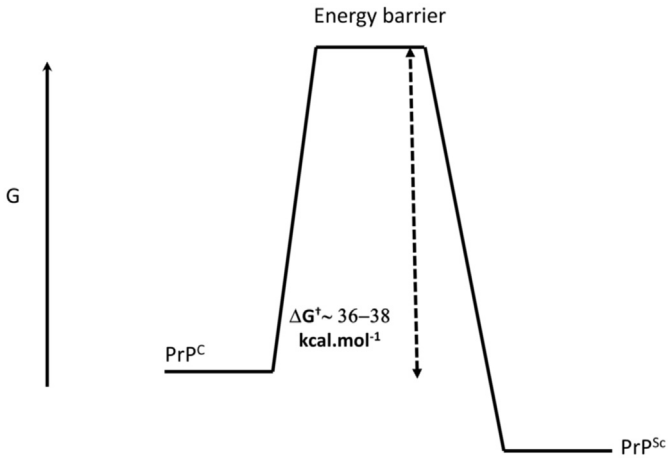

Fig. 2. Kinetic isolation of PrP^{Sc} from PrP^C (based on (Cohen and Prusiner, 1998).

What this means (Cohen and Prusiner, 1998) is that the 'normal' conformational macrostate of such proteins is not in fact that of the lowest free energy, and that its transition to the energetically more favourable 'rogue' state is thermodynamically favourable but under kinetic control, normally (in terms of transition state theory) with a very high energy barrier $\Delta G^{\dagger}$ of maybe 36–38 kcal mol^{-1} (Cohen and Prusiner, 1998) (Fig 2). Certainly, for a given and more tractable model sequence such as poly-L-alanine (Henzler Wildman et al., 2002), a β-sheet is demonstrably more stable than is an α-helix. However, the reversibility by pressure in some cases implies that the free energy change for oligomerisation is not particularly great (Foguel et al., 2003). The formal definition (Sipe et al., 2014) of an amyloid fibril (protein) is as follows: "An amyloid fibril protein is a protein that is deposited as insoluble fibrils, mainly in the extracellular spaces of organs and tissues as a result of sequential changes in protein folding that result in a condition known as amyloidosis."

Multiple states or conformations of amyloid/prion 'strains' are sometimes referred to in this field as 'polymorphisms' (Tycko, 2014), albeit they can have the same sequence (Tycko and Wickner, 2013). Importantly, they can be self-propagating (Chien et al., 2003, 2004; Colby and Prusiner, 2011; Collinge, 2010; Collinge and Clarke, 2007; Cushman et al., 2010; Eisenberg and Jucker, 2012; Gill, 2014; Greenwald and Riek, 2010; Le et al., 2015; Makarava and Baskakov, 2008; Moda et al., 2015; Petkova et al., 2005; Poggiolini et al., 2013; Sano et al., 2014; Toyama et al., 2007; Toyama and Weissman, 2011; Tycko, 2015; Weissmann, 2005; Wickner et al., 2014; Wiltzius et al., 2009). Even amyloidogenic proteins as small as $A\beta_{1\text{-}40}$ can adopt as many as five stable conformations (Fändrich et al., 2009; Kodali et al., 2010; Meinhardt et al., 2009; Reinke and Gestwicki, 2011), that can vary in terms of protofilament number, arrangement and structure (Fändrich et al., 2009), as can a model 17mer (Kammerer et al., 2004; Kammerer and Steinmetz, 2006; Verel et al., 2008). Clearly self-seeding can propagate similar conformations (Maji et al., 2009).

Many proteins are potentially amyloidogenic (Tzotzos and Doig, 2010). Thus, an increasing number of human diseases is known to be associated with misfolded or amyloid-type proteins (Chiti and Dobson, 2006; Herczenik and Gebbink, 2008; Knowles et al., 2014; Moreno-Gonzalez and Soto, 2011; Nienhuis et al., 2016; Olanow and Brundin, 2013; Rambaran and Serpell, 2008; Tipping et al., 2015). There are commonalities, in that amyloid proteins can cross-seed each other's polymerisation (e.g. (Frost and Diamond, 2010; Hu et al., 2015; Liu et al., 2007; Lundmark et al., 2005; Morales et al., 2013, 2015; Murakami et al., 2015; Murakami et al., 2014; Ono et al., 2012a; Soto et al., 2006; Westermark et al., 2009; Zhang et al., 2015a)). By contrast, "expression of two PrP^{C} moieties subtly different from each other antagonizes prion replication, and humans heterozygous for a common *Prnp* polymorphism at codon 129 are largely protected from CJD" (Aguzzi and Haass, 2003). Commonalities between prion protein misfolding and other protein misfolding diseases (AD, PD, ALS, etc (Prusiner et al., 2015)) that lead to amyloids are widely recognised; however, because the latter are not thought to be strictly infectious between individuals or across species, they have sometimes been referred to as prionoid diseases (Aguzzi and Lakkaraju, 2016; Ashe and Aguzzi, 2013). This said, their effects are clearly transmissible if injected (Eisele et al., 2015; Murakami et al., 2014, 2015; Soto, 2012; Soto et al., 2006; Sponarova et al., 2008; Westermark et al., 2009) (and see above). For completeness, in biotechnology, one should add that amyloid formation can interfere with the activity of protein biologics (e.g. (Nielsen et al., 2001a, 2001b, 2001c; Wang, 2005)), that bacterial inclusion bodies of recombinant proteins can also contain β-amyloid structures (e.g. (de Groot et al., 2009; Morell et al., 2008; Ventura and Villaverde, 2006; Wang, 2009; Wang et al., 2008)), and that at least some amyloid proteins are in fact beneficial to the host (Fowler et al., 2007).

β-structures are inherently stable (Tsemekhman et al., 2007). A characteristic "cross-β" X-ray diffraction pattern is observed from amyloid fibres (Maji et al., 2009; Tycko and Wickner, 2013). A diffuse reflection at 4.7–4.8 Å spacing comes from extended protein chains running roughly perpendicular to the fibril and spaced 4.7–4.8 Å apart. A more diffuse reflection at 10 Å illustrates that the extended chains are organized into sheets spaced ~10 Å apart (Eisenberg and Jucker, 2012; Langkilde et al., 2015; Morris and Serpell, 2012; Serpell, 2000; Stromer and Serpell, 2005). However, it is possible to form β-structures in multiple ways, that underlie the different more-or-less stable conformations (Eisenberg and Jucker, 2012).

The first kind of conformational variation or polymorphism (Eisenberg and Jucker, 2012) is packing polymorphism. Here, an amyloid segment packs in two or more distinct ways, producing fibrils with different structures and distinctive properties, most simply as a registration shift in which the two sheets forming the steric zipper in the second polymorph shift their interdigitation from that in the zipper of the first polymorph, e.g. by a couple of amino acids. The second structural model for strains is termed segmental polymorphism; here, two or more different segments of an amyloid protein are capable of forming spines, and do so, leading to different fibril structures. Finally, in a third type of amyloid polymorphism, heterosteric zippers, the zipper is formed from the interdigitation of nonidentical β-sheets.

As well as by quite subtle changes in sequence (Alexander et al., 2009; Gill, 2014), the fibril morphology is determined by environmental factors, such as pH (Kammerer et al., 2004; Verel et al., 2008), charge-neutralising polyanions (Groveman et al., 2015; Silva et al., 2011), temperature (Kammerer et al., 2004; Verel et al., 2008), agitation (Ladner-Keay et al., 2014), salts (Klement et al., 2007), lipids (Gursky, 2015; Levine et al., 2015), other co-solutes (Chiti et al., 1999), small molecule additives (Doig and Derreumaux, 2015) or even quite large protein sequences (and see below). To this end, a bacteriophage motif may be significantly anti-amyloidogenic and capable of remodelling formed amyloids (Krishnan et al., 2014). At all events, the hallmark of these kinds of amyloidogenic behaviour (Jucker and Walker, 2013) is the conversion of a soluble protein, typically a monomer, into an insoluble form that typically forms oligomers, protofilaments and then insoluble fibrils.

In summary, it is increasingly recognised that proteins can self-organise into fibrils that require only a conformational change (no sequence changes) and that these can vary as a function of both the sequence and environmental conditions. However, many of these processes occur on a rather sluggish timescale.

Another area in which a soluble precursor (fibrinogen) is converted into insoluble fibres (fibrin) occurs during the terminal stages of blood clotting. Perhaps surprisingly, this has not really been seen as a useful model for prion and amyloidogenic diseases, and certainly fibrin alone cannot 'seed' the growth of fibrin molecules, as each fibrinogen molecule added to the growing fibril requires that thrombin first releases two fibrinopeptides (see below). It is also a process that is necessarily and typically considerably quicker than classical amyloidogenesis. However, the main purposes of the present review are (i) to highlight the commonalities that do exist, and (ii) to illustrate in particular the very substantial changes in fibre morphology, including the recently discovered amyloid formation, that can be elicited by simple, and in many cases highly substoichiometric additions of small molecules. We believe that this will admit a substantial and useful cross-fertilisation of these fields. We highlight in particular the facts that (a) blood is much more easily available and amenable to study

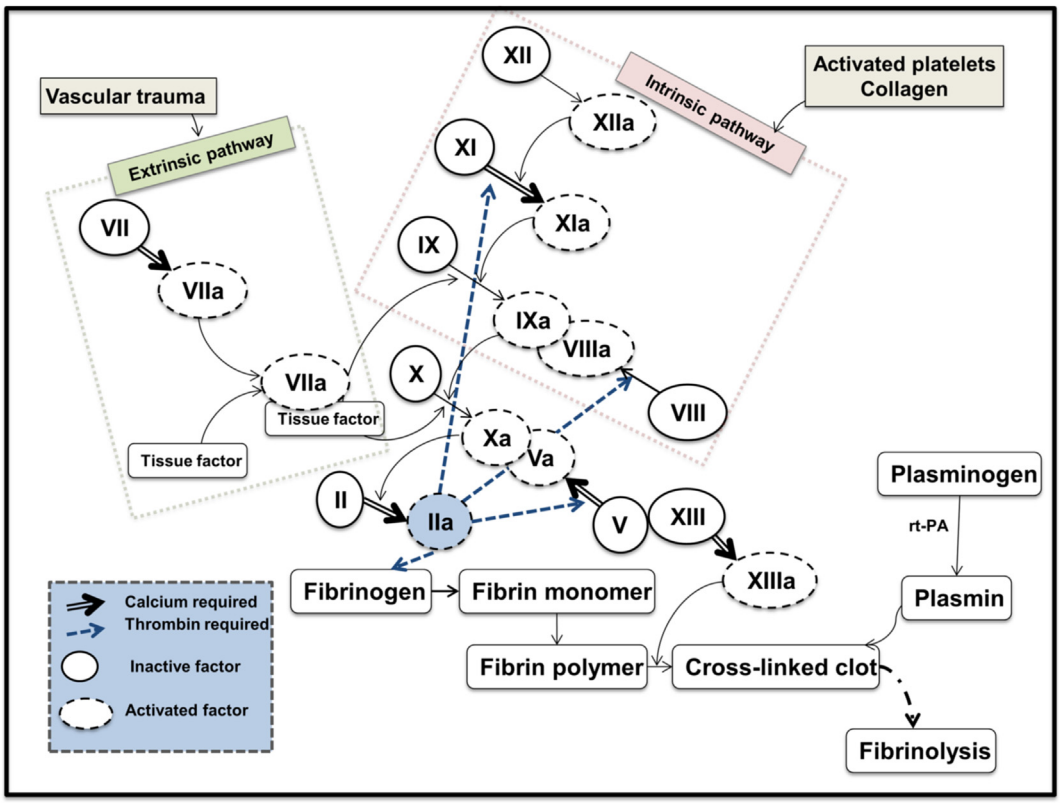

Fig. 3. The coagulation cascade showing the final conversion of fibrinogen to fibrin.

than are tissue materials, and (b) that at least some ligands, such as bacterial lipopolysaccharide (LPS), may be involved in both blood clotting and amyloidogenesis, and thus contribute to shared aetiologies. A preprint has been lodged in bioRxiv (Kell & Pretorius 2016).

2. The terminal stages of normal blood clotting: fibrinogen, fibrin and thrombin

The terminal stage of the coagulation cascade involves the conversion of fibrinogen to fibrin strands, and this involves a number of regulated steps (see Fig 3). Both the expansion and strength of the final clot is finely regulated and depends mostly on the conversion of fibrinogen to fibrin under the enzymatic action of thrombin, which (apart from a subsequent crosslinking induced by the transglutaminase factor XIII) is the final step in the cascade.

Fibrinogen circulates at high concentrations 2–4 $mg.L^{-1}$ (Walton et al., 2015) or at about 9 mM in the plasma (Ferri et al., 2002; Neeves et al., 2010), with a molecular mass of around 340 kDa. It has a centrosymmetric, trinodular, S-shaped structure that is 46 nm in length and 4.5 nm in diameter (Guthold et al., 2007). During coagulation, thrombin cleaves two N-terminal peptides from the Aα- and Bβ-chains, promoting the formation of protofibrils and subsequently fibrin fibres (Litvinov et al., 2007; Undas and Ariëns, 2011).

The fibrinogen protein consists of two sets each of three polypeptide chains (Aα, Bβ, $\gamma)_2$ (Walton et al., 2015), linked by 29 S-S bonds (Litvinov et al., 2012) that has the basic structure shown in Fig 4.

The main features are:

- A single central E-region, containing 6 N-termini and fibrinopeptides A and B
- Two D-regions flanking the E-region; each D-region contains a globular β C-terminal domain (β197–461; called βC) and the globular γ C-terminal domain (γ143–411; called γC), both of which consist of a β-sheet core flanked by a few small α-helices (Guthold et al., 2007).
- Two coiled coils consisting each of three α-helices; these coils connect the E– and D-regions.
- There are also 29 disulphide bonds that acts as stabilizers; and 5 of these disulphide bonds are within the central E-nodule that forms a link between the two halves of the molecule.
- There are also 4 disulphide rings, consisting of 3 disulphide bonds that link the α-to the β-chain, the α-to the γ-chain, and the β-to the γ-chain. This forms a supporting unit that keeps the three α-helices in the coiled coils together in each fibrinogen molecule; 1 ring at each end of the two coiled coils.
- Twelve intra-chain disulphide bonds, 3 in each of the 2 globular βC domains of the D-regions, 2 in each of the two globular γC domain of the D-regions, and one in each of the two αC domains.

Thrombin cleaves the fibrinogen, resulting in the fibrin monomers containing Aα, Bβ and γ polypeptides, which are then curved into the central E-region containing the 2 distal D-regions (Yang et al., 2001; Yeromonahos et al., 2010). Fibrin monomers are formed on the removal of 2 pairs of fibrinopeptides (fibrinopeptide A and B from the N-termini of the Aα and Bβ chains), converting it into a fibrin monomer that immediately polymerizes by self-assembly, to form a complex or a meshwork of fibrin fibres. Importantly, however, the fibrin monomer maintains major structural features of fibrinogen, including the coiled-coils (Litvinov et al., 2012). When the 2 fibrinopeptides are removed from the N-terminal region of the Aα- and Bβ-chains, knoblike binding sites A and B, are exposed (Guthold et al., 2007). Finally, an insoluble fibrin gel complex is formed when the fibrin strands aggregate and

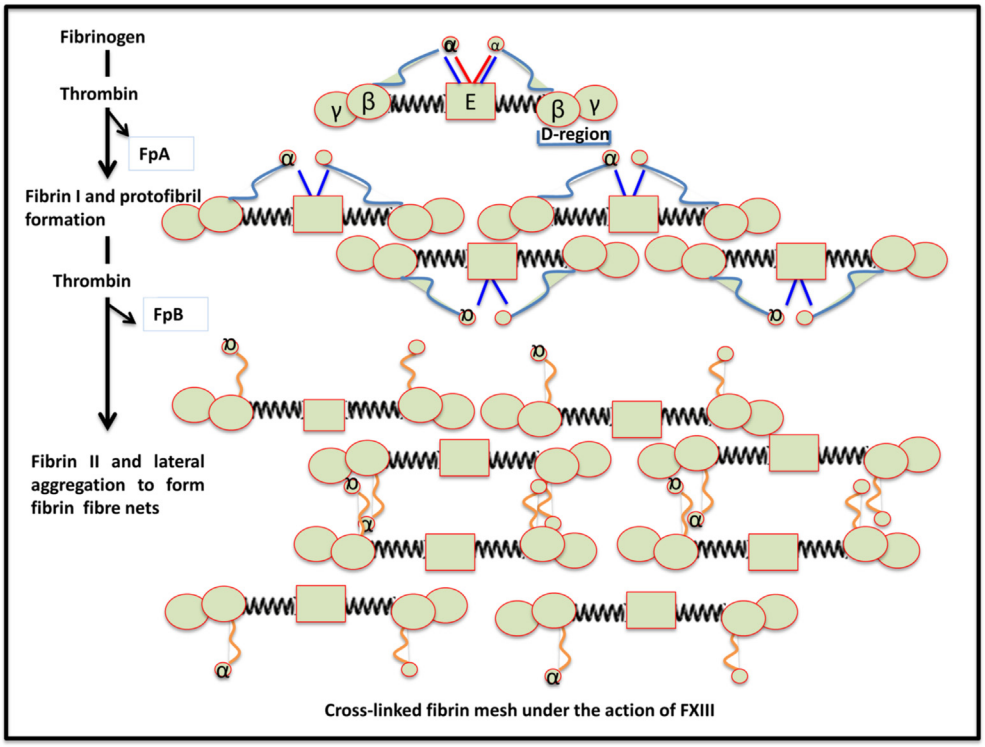

Fig. 4. Diagrammatic representation of fibrinogen packaging into the final product, the cross-linked fibrin mesh.

form cross-links through the actions of thrombin-catalyzed factor XIIIa (Dickneite et al., 2015; Ferry and Morrison, 1947; Fowler et al., 1981; Neeves et al., 2010; Phillips et al., 2003; Weisel, 1986).

Plasma FXIII (fibrin stabilizing factor) is a plasma transglutaminase (Dickneite et al., 2015) and consists of two catalytic subunits (FXIII-A) and two non-catalytic subunits (FXIII-B) that are tightly connected in a non-covalent, heterotetramer (FXIII-A_2B_2). All FXIII-A_2B_2 in the circulation are bound to fibrinogen (Walton et al., 2015). FXIII-A_2B_2 is activated by thrombin-catalyzed release of N-terminal peptides from the FXIII-A subunits and calcium-mediated dissociation of the FXIII-B subunits, yielding activated FXIII-A_2 (or FXIIIa) (Walton et al., 2015).

Both plasma- and platelet-derived FXIIIa catalyse the formation of ε-N-(γ-glutamyl)-lysyl crosslinks within fibrin (Walton et al., 2015) and this crosslinking stabilizes fibrin fibres and therefore clots (Walton et al., 2015). XIIIa has profound effects on fibrin integrity and it seems that γ- and α-chain crosslinking make distinct contributions to clot function and structure (Richardson et al., 2013; Standeven et al., 2007). FXIIIa therefore plays in important role in the regulation of thrombus stability, regulation and cell-matrix interactions, including wound healing (Richardson et al., 2013).

Recently, it was found that unperturbed (human) fibrin contains 30± 3% α-helices, 37± 4% β-sheets, and 32± 3% turns, loops, and random coils (Litvinov et al., 2012). As discussed in detail later, under certain physiological (and also pathological) conditions, fibrin clots may undergo deformation, where molecular unfolding may occur (Litvinov et al., 2012; Zhmurov et al., 2011, 2012). Secondary structural alterations including the α-helices to β-sheets transition, is a common mechanism of protein structural rearrangement. Increased force can result in the uncoiling of the α-helices (or coiled coils) resulting in an increase of β-sheets. However, the simple binding of the fibrinopeptides to their corresponding holes on the D-regions does not result in any significant increase in β-sheets (See Fig 5 for a visual representation of when the formation of increased β-sheets and the uncoiling of the α-helices does occur, e.g. under mechanical loading.)

These deformations affect the viscoelasticity at both the fibre and molecular levels and will translate into functional changes at the whole clot level. They also have implications for systemic changes of coagulation. Therefore, during the molecular extension of fibrin, α-helix to β-strand conversion occurs in coiled-coils and during both mechanical elongation and compression of fibrin clots, a rearrangement of the secondary clot structure occurs, comprising mainly the α-helix-to-β-sheet transition (Litvinov et al., 2012). The authors suggested that the α-β transition followed by formation of an intermolecular β-sheet structure and protein aggregation could be a common mechanism underlying the different types of fibrin deformation (Litvinov et al., 2012). Here, we suggest that this may be the fundamental underlying reason for different fibrin fibre ultrastructures that we have previously reported on, where we found a changed macroscopically observable fibrin fibre structure during various systemic inflammatory conditions.

Many excellent reviews exist on the mechanisms of clot formation and basic structure (e.g. (Cilia La Corte et al., 2011; Undas, 2014; Undas and Ariëns, 2011; Undas et al., 2011; Weisel, 2005, 2007; Wolberg, 2007; Wolberg, 2012)), fibrinolysis (Chapin et al., 1989; Longstaff and Kolev, 2015; Undas et al., 2008), and the importance of clotting in vascular diseases (Ariëns, 2011, 2013; Bridge et al., 2014). Because of this, we can be relatively brief, and focus on the nub of our review, which is the argument that, like prions, fibrinogen can, under certain circumstances, form beta-sheet-rich amyloid fibrils.

3. Methods for determining the clotting process

Studying clot formation and degradation, using either plasma or whole blood, is important in the treatment of hyper-as well as hypocoagulability, and both optical and rheological/viscoelastometric methods have been developed (e.g. (Bates and Weitz, 2005;

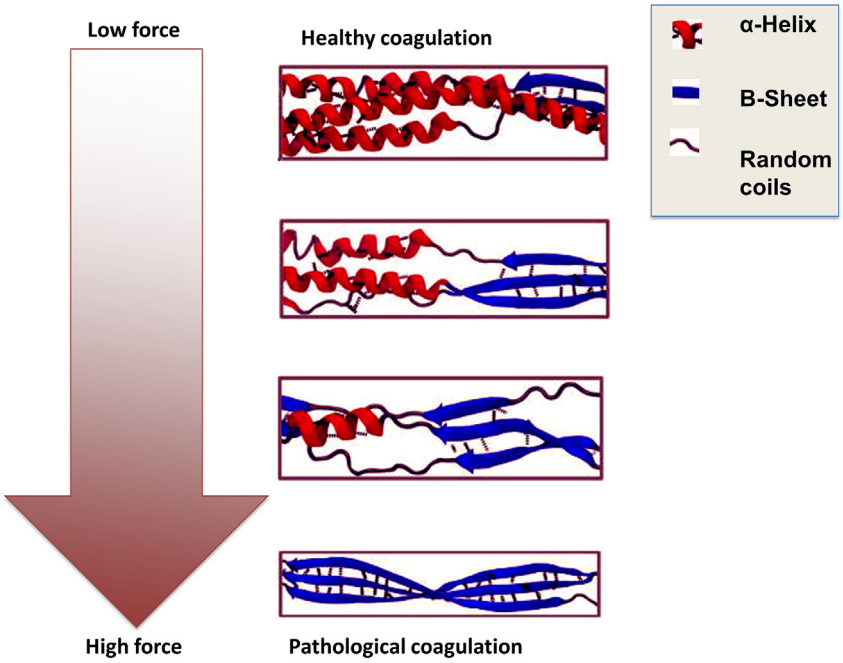

Fig. 5. The α-helices to β-sheets phase transition in fibrin formation under deformation of e.g. low (healthy coagulation) and high force (pathological coagulation) (adapted from (Zhmurov et al., 2012)).

Berntorp and Salvagno, 2008; Chitlur, 2012; Ganter and Hofer, 2008; McMichael and Smith, 2011)); for a recent review, see (Kell and Pretorius, 2015b). Currently, visco-elastic technologies are mainly used as point-of-care tests with immediately-available results; these include prothrombin time (PT), activated partial thromboplastin time (APTT), thromboelastography (TEG) and thromoboelastometry (ROTEM). Analyses that use plasma obtain results based on PT and APTT (Johansson et al., 2009); however, PT and APTT only test the coagulation protein component of the system, and results have to be interpreted carefully in the context of the clinical presentation and assay limitations (Chee, 2014). Consequently, we rather favour the use of viscoelastic haemostatic methods such as TEG (Afshari et al., 2011; Bolliger et al., 2012; Johansson et al., 2009; Reikvam et al., 2009; Sankarankutty et al., 2012), ROTEM (Afshari et al., 2011; Sankarankutty et al., 2012; Sørensen and Ingerslev, 2005; van Veen et al., 2009) and the Sonoclot (Hett et al., 1995; Kjellberg and Hellgren, 2000; Sharma et al., 2013).

In the past, EP's laboratory has focussed specifically on using the TEG (Bester et al., 2015; de Villiers et al., 2016; Nielsen and Pretorius, 2014a, 2014b; Nielsen et al., 2015; Swanepoel et al., 2015). See Table 1 for a comprehensive list of measurements that can be done using thromboelastography.

Another important technique that we have combined with the TEG results, with great success, is scanning electron microscopy of fibrin fibre structure (Bester et al., 2015; de Villiers et al., 2016; Kell and Pretorius, 2015a, 2015b; Nielsen and Pretorius, 2014a; Nielsen and Pretorius, 2014b; Nielsen et al., 2015; Potgieter et al., 2015; Pretorius et al., 2014a, 2016b, 2016c; Pretorius et al., 2013; Swanepoel et al., 2015). These methods give a visual representation of clot structure, where the fibrin packaging can be studied at high resolution and magnification, and have illustrated the very great differences that can be observed in plasma from diseased vs healthy controls. As mentioned in the previous paragraphs, PT, PTT, TEG, as well as ROTEM have been used successfully as point-of-care methods, while electron microscopy has been used mostly in the laboratory. However, the usefulness of combining the technologies in an integrated approach is clear (de Villiers et al., 2016; Pretorius et al., 2016d; Swanepoel et al., 2015).

Table 1
TEG parameters typically generated for whole blood and platelet poor plasma (Bester et al., 2015; de Villiers et al., 2016).

Thromboelastic parameters		
R value: reaction time	Minutes	Time of latency from start of test to initial fibrin formation (amplitude of 2 mm); i.e. initiation time
K: kinetics	Minutes	Time taken to achieve a certain level of clot strength (amplitude of 20 mm); i.e. amplification
A (Alpha): Angle (slope between thetraces represented by R and K) (	Angle in degrees	The angle measures the speed at which fibrin build up and cross linking takes place, hence assesses the rate of clot formation; i.e. thrombin burst
MA: Maximal Amplitude	mm	Maximum strength/stiffness of clot. Reflects the ultimate strength of the fibrin clot, i.e. overall stability of the clot
Maximum rate of thrombus generation (MRTG)	$Dyn.cm^{-2}.s^{-1}$	The maximum velocity of clot growth observed or maximum rate of thrombus generation using G, where G is the elastic modulus strength of the thrombus in dynes per cm^{-2}
Time to maximum rate of thrombus generation (TMRTG)	Minutes	The time interval observed before the maximum speed of the clot growth
Total thrombus generation (TTG)	$Dyn.cm^{-2}$	The clot strength: the amount of total resistance (to movement of the cup and pin) generated during clot formation. This is the total area under the velocity curve during clot growth, representing the amount of clot strength generated during clot growth
Lysis 30 (LY30)	%	Percentage lysis obtained 30 min after MA

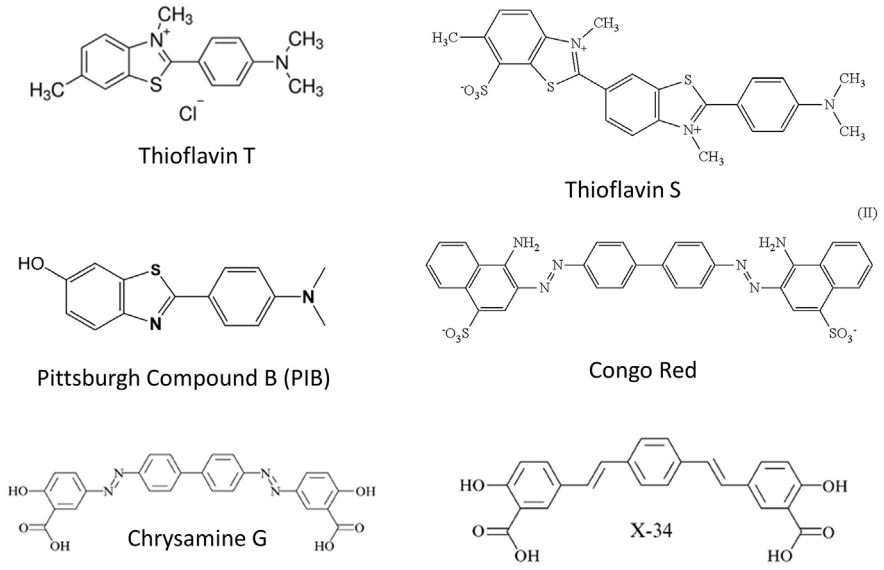

Fig. 6. Examples of amyloid staining reagents.

3.1. Optical methods based on fluorescence and birefringence

As with fluorescent proteins such as GFP, the ability to detect amyloid (and cross-β motifs more generally) by optical means would improve their ease of study enormously (Hammarström et al., 2013). Fortunately, a number of appropriate dyes are known (Fig 6).

Congo Red (Bély and Makovitzky, 2006; Frid et al., 2007; Howie and Brewer, 2009; Howie et al., 2008; Howie and Owen-Casey, 2010; Inouye and Kirschner, 2005; Kelényi, 1967; Maezawa et al., 2008; Nilsson, 2004; Wu et al., 2012a) (CR) was one of the first dyes known to bind to amyloid (Puchtler and Sweat, 1966). Its name derives (Steensma, 2001) from the marketing activities of the Berlin-based AGFA textile dyestuff company in 1885, following various geopolitical events of that time, but otherwise has no connection with central Africa. Bennhold (Bennhold, 1922) was the first to describe its binding to amyloid. This induces a characteristic shift in CR's maximal optical absorbance from 490 nm to 540 nm, and rather variable (Howie, 2015; Howie and Brewer, 2009; Howie et al., 2008; Howie and Owen-Casey, 2010) birefringence and dichroism. As Howie and Brewer rather nicely put it (Howie and Brewer, 2009), "Amyloid stained by Congo red has striking optical properties that have mostly been badly described and inadequately explained", although in general terms the birefringence clearly reflects the binding to the oriented β-sheets, with the orientation being increased by the practice of making smears. There is evidence for the particular involvement of histidine residues (Inouye and Kirschner, 2005; Inouye et al., 2000). Because the colours seen vary rather markedly with the relative orientations of polariser and analyser in the birefringence measurements (Howie, 2015; Howie and Brewer, 2009; Howie et al., 2008; Howie and Owen-Casey, 2010), and although apparently preferred as a 'gold standard' by histologists, CR is seen as a stain that is less than perfectly reproducible, and at least for research it has largely been overtaken by fluorescent stains. This said, we note with interest a recent 'smartphone' assay application (Acestor et al., 2016; Jonas et al., 2016; Rood et al., 2015).

3.2. Thioflavin S, thioflavin T and derivatives

The thioflavin stains (based on a thiazole nucleus) probably count most nearly as "God's gift to students of amyloid and amyloidogenesis". Free thioflavin T (ThT) fluoresces faintly with excitation and emission maxima of 350 and 440 nm, respectively, whereas upon interaction with amyloid fibrils a substantially enhanced ThT fluorescence is observed, with excitation and emission maxima at about 440/450 and 480/490 nm, respectively (Groenning, 2010; Khurana et al., 2005; Kuznetsova et al., 2016, 2012a, 2012b; LeVine, 1997; LeVine, 1999; Lindberg et al., 2015; Naiki et al., 1989; Palhano et al., 2013; Picken and Herrera, 2012; Robbins et al., 2012; Sulatskaya et al., 2011, 2012; Wolfe et al., 2010; Younan and Viles, 2015; Zhang and Ran, 2013). Table 2 summarises the wavelengths used in a number of studies.

As with CR, the fluorescence enhancement is caused by binding to oriented β-rich fibrils. Fig 7 shows the conversion of typical amyloid-free fibrin fibres to highly-amyloid-rich ones as judged by their staining with ThT, added to plasma from a patient with thromboembolic stroke (Fig 7B) and compared with the same treatment of plasma from a matched, healthy control. The difference is rather striking.

As a dibenzothiazole dye (Wu et al., 2007), Thioflavin S (ThS) is a somewhat extended version of ThT (Fig 6). We are not aware of any

Table 2
Wavelengths that have commonly been used for excitation and emission when assessing Thioflavin T interaction with β-amyloids.

Excitation (nm)	Emission (nm)	References
455	485	(Ban et al., 2003)
440	490	(Berthoumieu et al., 2015)
440	485	(Biancalana et al., 2009)
435	480	(Di Carlo et al., 2015)
450	460–600	(Groenning et al., 2007)
440	460–570	(Jha et al., 2011)
440	490	(Jha et al., 2014)
450	482	(LeVine, 1993)
440/20	485/20	(LeVine, 1997)
440–450	480–490	(Lindberg et al., 2015)
450	482	(Naiki et al., 1989)
445	485	(Ozawa et al., 2011)
440	485	(Palhano et al., 2013)
450	480	(Sabaté and Ventura, 2013)
449	480	(Sulatskaya et al., 2011)
440	<600	(Younan and Viles, 2015)

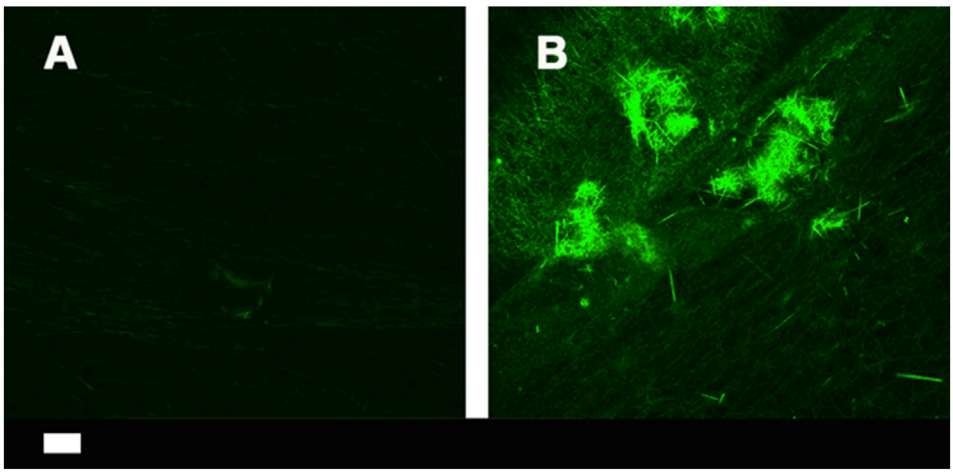

Fig. 7. Fibrin fibres from a healthy individual **(A)** and an individual who had suffered a thromboembolic stroke **(B)**, stained with ThT (5 μM exposure concentration) and viewed using a confocal microscope. Scale bar: 10 μm.

direct comparisons of THS and ThT, though ThS has been improved for tissue staining (Sun et al., 2002). Consequently, it may seem sensible to use the smaller dye. Protein transporters are required to get xenobiotics into cells (Dobson and Kell, 2008; Kell et al., 2011, 2013; Kell and Oliver, 2014). For tissue staining, even ThT does not penetrate the blood-brain barrier, and a neutral version known as Pittsburgh compound B (PIB) (Fig 6) has been developed that can (Mathis et al., 2003; Murray et al., 2015; Wu et al., 2011). (Based on its structure and the analyses presented elsewhere (O'Hagan and Kell, 2015; O'Hagan and Kell, 2016; O'Hagan et al., 2015), the three Recon 2(.2) metabolites (Swainston et al., 2013, 2016; Thiele et al., 2013) and marketed drugs to which it is most similar are given in Fig 8.) However, while its ^{11}C-derivative has been widely used in PET imaging of fibrils (e.g. (Driscoll et al., 2012; Grimmer et al., 2009; Mathis et al., 2007; Murray et al., 2015; Resnick et al., 2010; Wu et al., 2011)), PIB lacks the large optical absorbance shift and fluorescence enhancement characteristic of ThS and ThT (Wu et al., 2011).

Other amyloid-selective dyes that have been used include X-34 (Excitation 400nm/Emission 455 nm), which is in fact a fluorescent derivative of CR (Ikonomovic et al., 2006; Link et al., 2001; Styren et al., 2000), chrysamine G (Kang and Han, 2001; Klunk et al., 1994) (Fig 6) (which is excited at 386 nm) and ANCA (excitation 380–430, emission 525–550). Since most of these latter are not commercially available, it is not obvious that these dyes bring great benefits over ThT. This said, it is normally desirable to be able to excite nearer the red (Kovalska et al., 2012; Ono et al., 2012b; Rajasekhar et al., 2016) or beyond (Guo et al., 2014; Staderini et al., 2015; Watanabe et al., 2013; Yuan et al., 2013b; Zhang et al., 2015b) to decrease autofluorescence, and such dyes are likely to be very useful as they become more widely available.

In an interesting development, Stefansson and colleagues

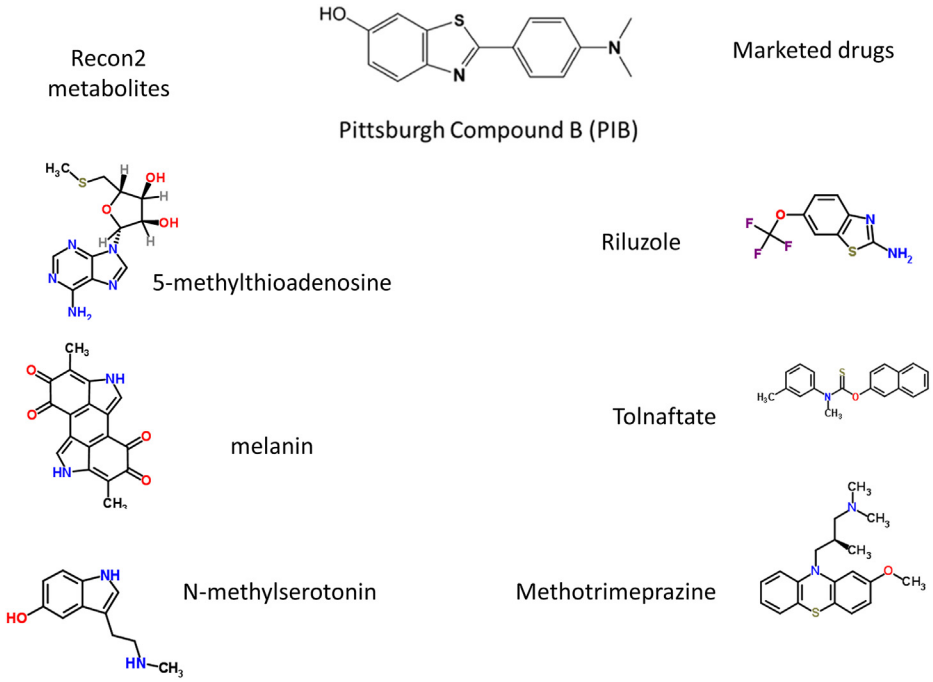

Fig. 8. The three endogenous metabolites and marketed drugs most closely related to PIB, as assessed using the MACCS encoding (Durant et al., 2002) and the Tanimoto distance.

(Stefansson et al., 2012) noted that (i) the thiazole moiety is critical to binding (Wolfe et al., 2010), and (ii) that a number of modern, sensitive DNA-intercalating dyes also contain the thiazole nucleus. They showed (Stefansson et al., 2012) that these dyes too would bind to β-amyloid fibrils, albeit not normally (but cf (Lindberg and Esbjorner, 2016)) with quite with the same fluorescence enhancement as shown by ThT. However, they could be used in combination with ThT to increase the Stokes shift (via fluorescence resonance energy transfer) quite hugely into the red. Note though that the binding of these (Reuter and Dryden, 2010) and related dyes (Twist et al., 2004) to double-stranded DNA can be detected at the level of the single molecule, so such DNA must be absent. There is no doubt that continuing improvements in dye development will be of considerable value to the field.

3.3. *Luminescent conjugated thiophenes*

In an interesting and important development, Nilsson and colleagues (e.g. (Berg et al., 2010; Klingstedt et al., 2011, 2013a; Klingstedt and Nilsson, 2012; Nilsson et al., 2005, 2006, 2007, 2009, 2010, 2012; Shirani et al., 2015; Simon et al., 2014; Sjölander et al., 2015, 2016)) have introduced a series of luminescent oligothiophenes and polythiophenes. As well as possessing excellent optical properties, they seem preferentially to stain the smaller oligomers (Klingstedt and Nilsson, 2012) that may be more cytotoxic (see below). They can also be used to discriminate different fibres and conformational states optically (e.g. (Åslund et al., 2007, 2009; Klingstedt et al., 2013a, 2013b, 2015; 2012; Magnusson et al., 2014)). Consequently, these and related molecules seem to be well worth exploring as part of the next generation of amyloid-selective dyes, not least in the context of super-resolution (Ries et al., 2013).

4. The conversion of fibrinogen to fibrin is normally not a transition from α-helices to β-sheets except in special circumstances that include mutants

A clear characteristic of the conversion of amyloidogenic proteins to genuine insoluble amyloids is the conversion of structures with (typically) predominantly α-helices to structures with a (much) greater β-sheet content. The obvious question is to what extent is this similarly true in normal and abnormal clotting processes?

As seen in the section on normal blood clotting, the chief mechanism involves a 'knobs and stalks' interaction (that includes the ability to repair fibrils isoenergetically (Chernysh et al., 2012)), and that does not of itself require, nor does it seemingly provide, any major conformational changes in the secondary structure of the fibrinogen monomers (Averett et al., 2008, 2009; Protopopova et al., 2015; Weisel, 2005; Yermolenko et al., 2011). In a similar vein, normal blood clotting is not considered to be an amyloidogenic process, except in very rare cases of particular mutants of the fibrinogen a chain (Benson et al., 1993; Gillmore et al., 2009; Haidinger et al., 2013; Hamidi Asl et al., 1997; Picken, 2010; Serpell et al., 2007; Stangou et al., 2010).

5. Mechanical stretching can induce an α-to-β transition in a large variety of biopolymers

As judged by infrared spectroscopy of the various amide bands, standard human fibrin is about 30% α-helix, 40% β-sheet and 30% turns (Bramanti et al., 1997), similar to the numbers given (above) by Litvinov et al. (Litvinov et al., 2012). This percentage changes with pressure and mechanical unfolding (Litvinov et al., 2012; Zhmurov et al., 2011, 2012), but only at extremes of stretching (that apparently do not happen in normal clot formation) are the mechanical properties of fibrin considered to reflect an α-to-β transition (Guthold et al., 2007; Kreplak et al., 2004; Liu et al., 2010; Miserez and Guerette, 2013). Specifically, at a certain extension there is what amounts to a phase transition. To this end, there were also some striking nonlinearities noted in the detailed studies of Münster and colleagues (Münster et al., 2013) and of Kim and colleagues (Kim et al., 2014).

It is of some interest that mechanical forces can also be used to effect an α-to-β transition in prions (Tao et al., 2015) and a variety of other elastomeric biopolymers (Feughelman, 2002; Hearle, 2000; Miserez and Guerette, 2013; Qin and Buehler, 2010), not least keratin (Bendit, 1957, 1960; Kreplak et al., 2004; Paquin and Colomban, 2007). It is particularly noteworthy that after two- and three-fold longitudinal stretching the median fibre diameter and pore area in SEM images of fibrin decreased two-to three-fold (Varjú et al., 2011), just as in a number of the disease states mentioned above, and that this conferred proteolytic resistance to the fibrin, What the above examples tell us is that under normal circumstances human fibrin does not adopt a form that has a β-sheet content greater than ~40%, but that it can indeed do so under the appropriate circumstances. What we shall see below, is that these are considerably more common than had previously been surmised.

5.1. *Effects of flow on fibrin properties*

The above studies involved mechanical stretching, but (given that blood does flow in the circulation) there has been some interest in the effects of flow (velocity) on fibrin structure. Increases in fibre thickness. Hints of β-sheet formation induced by flow can be seen in (Badiei et al., 2015), while in a very striking study, Campbell et al. (Campbell et al., 2010). saw a huge increase in the flow-induced diameter of fibrin fibres, from a mean of 79–226 nm.

6. When clotting goes wrong: hypercoagulability and hypofibrinolysis in chronic, inflammatory diseases

In inflammatory conditions, hypercoagulability, as well as hypofibrinolysis is a common phenomenon and both are seen as coagulopathies; see (Kell and Pretorius, 2015b) for a table with a comprehensive list of inflammatory diseases with both known hypercoagulable and hypofibrinolytic characteristics. Our particular interest has been the study of clot structure using scanning electron microscopy, and we have noted that this method shows us precisely the diameter of individual fibrin fibres, as well as the general clot architecture (e.g. (Lipinski and Pretorius, 2013a, 2013b; Lipinski et al., 2012b; Pretorius, 2011; Pretorius et al., 2014a; Pretorius and Lipinski, 2013a; Pretorius and Oberholzer, 2009; Pretorius et al., 2010a, 2010b, 2011a, 2011b)). We and others have shown that the diameter of 'typical' healthy fibrin fibres is 80–110 nm (Bester et al., 2015; Kell and Pretorius, 2015b; Pretorius et al., 2011c; Weigandt et al., 2012) (those of most amyloidogenic proteins are more like 10–20 nm or less, e.g. (Engel et al., 2008; Foguel et al., 2003; Ivanova et al., 2004; Klement et al., 2007; Kollmer et al., 2016; Uversky et al., 2001)), while during inflammation, clot diameter changes. It may be increased, as seen in Alzheimer's type dementia (Bester et al., 2015), or decreased as seen in stroke (Pretorius et al., 2011c). Up to now we have had no knowledge of the exact molecular conformational changes (e.g. the α-helices and β-sheets) that happen during inflammation; we have just reported on the more macroscopically observable structural changes that are visible in the different conditions (See Fig 9). Now it has become clear that the exact changes that happen during inflammation in the α-helix and β-sheet interaction involve major changes in secondary structure, and might be of great importance

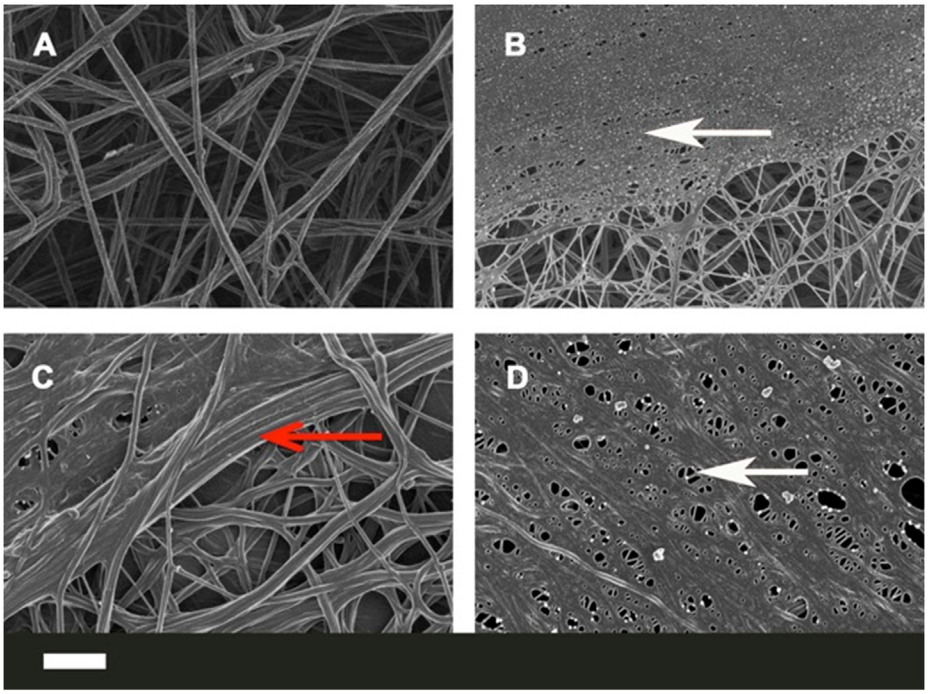

Fig. 9. Representative micrographs of different inflammatory conditions. **A)** Healthy fibrin fibre structure; **B)** thromboembolic stroke; **C)** Alzheimer's type dementia; **D)** Type II diabetes. White arrows: fine netted areas; Red arrow: areas where fibrin fibres are thicker. Scale bar: 1 μm.

to understand both hypercoagulability and hypofibrinolysis.

In vivo, as part of normal wound healing, the clot is removed via the fibrinolytic system and this process is mediated by the serine protease plasmin, which cleaves the fibrin molecule at specific sites (Bucay et al., 2015; Draxler and Medcalf, 2015) to form a variety of degradation products collectively referred to as D-dimer (Adam et al., 2009; Walker and Nesheim, 1999). (Whether D-dimer can adopt a β-sheet of amyloid form is apparently unknown, and its concentration varies but little during amyloidosis (Suga et al., 2012)). During fibrin polymerisation, normally cryptic plasminogen and plasmin binding sites are exposed. These binding sites are situated on the αC regions that contain lysine-dependent tPA- and plasminogen-binding sites (Bucay et al., 2015; Medved and Nieuwenhuizen, 2003). During fibrinolysis, plasmin initially cleaves the αC regions, and then cleaves the three polypeptide chains connecting the E-domains and the D-domains (Bucay et al., 2015; Nieuwenhuizen, 2001). The exact process of fibrinolysis is controlled by various structural arrangements and physical properties of the clot itself. These properties include clot density, stiffness and fibrin fibre diameter (Collet et al., 2003; Veklich et al., 1998; Weisel, 2007). Bucay and co-workers in 2015 found that if fibres are exposed to plasmin, thin fibres are easily cleaved, and that thicker fibres grew in length during fibrinolysis. Therefore the lytic susceptibility of a fibre is directly related to the intrinsic strain on the fibre resulting from the polymerisation process (Bucay et al., 2015). Here we also suggest that the lysine-dependent tPA- and plasminogen-binding site accessibility on the fibrin fibres will be crucial for successful fibrinolysis and therefore the arrangement of the α-helix and β-sheets will be of fundamental importance in this process. The difficulty or resistance of hydrolysis of abnormal fibrin clots can be directly compared to this 'hypohydrolysis" (proteinase K resistance) characteristic of PrP^{Sc}, discussed in detail above.

As summarised by Campbell and colleagues (Campbell et al., 2010), diameter *per se* can affect fibrinolysis rates: "Fibre diameter and network density play significant roles in clot dissolution (Weisel and Litvinov, 2008). Compared to thin fibres, thick fibres support faster plasmin generation rates. Plasmin lyses fibrin via laterally transecting individual fibres. Thin fibres lyse faster than thick fibres; however, coarse networks of thick fibres lyse faster than tight networks of thin fibres (Collet et al., 2000)." However, we suggest here that it may also be secondary structure that plays the major role.

One of the most damaging forms of hypercoagulation is known as disseminated intravascular coagulation (Asakura, 2014; Bick, 2002; Kaneko and Wada, 2011; Levi and van der Poll, 2013a; Wada et al., 2014). It is essentially a runaway form of hypercoagulation, and it too may be induced by LPS (endotoxin) (Asakura, 2014; Duburcq et al., 2015; Wu et al., 2012b, 2014; Yu et al., 2013). There is significant evidence that it can itself lead to multiple organ failure and death (Gando, 2010). It does not yet seem to be known, but seems probable, that the form of fibrin in DIC is indeed a β-amyloid.

Clot retraction. Clot retraction (contraction) is a physiological process initiated by platelets that results in compaction of the fibrin network and expulsion of the majority of serum from the clot - together with the majority of unbound plasminogen, typically over a 24 h period *in vivo* (Cines et al., 2014). It reflects in part the crosslinking of fibrin effected by Factor XIII (Hethershaw et al., 2014; Kasahara et al., 2010, 2013). According to Weisel (Weisel, 2011), commenting on the important Varjú paper (Varjú et al., 2011), so-called retracted clots are much more resistant to lysis (Kunitada et al., 1992; Šabovič and Blinc, 2000; Sabovic et al., 1989), and retracted clots probably provide a useful model for events such as stroke. Clots are much stiffer in diseases such as multiple myeloma (Carr and Zekert, 1994; Lackner et al., 1970). It is not yet apparently known whether clot retraction is accompanied by β-sheet formation.

7. Mutual effects of fibrin(ogen) on β-amyloid in Alzheimer's disease

We rehearsed above how there was a limited (non-zero) cross-

reactivity between heterologous amyloidogenic proteins, and an example of particular interest is given by the interaction between fibrin(ogen) and β-amyloid, as developed by Strickland and colleagues (Ahn et al., 2010, 2014; Cortes-Canteli et al., 2015; Cortes-Canteli et al., 2010; Cortes-Canteli and Strickland, 2009; Cortes-Canteli et al., 2012; Paul et al., 2007; Zamolodchikov and Strickland, 2012). We rehearse their highly important arguments and findings in some detail.

As pointed out by Paul and colleagues (Paul et al., 2007), fibrinogen is present in the brains of AD patients (Fiala et al., 2002), but the pathologic significance is or was not known. Using mutant mice, they showed the definite contribution of fibrin to the aberrant pathology (Paul et al., 2007). As is well known, the extracellular plaques in the AD brain are composed mainly of a 40–42 amino acid peptide, the β-amyloid or amyloid-β (Aβ) peptide that is derived proteolytically from the N-terminus of the so-called amyloid-β precursor protein (APP). There is little doubt (the 'amyloid hypothesis' (Eisele et al., 2015; Hardy and Selkoe, 2002; Hardy and Higgins, 1992; Jonsson et al., 2012; Minter et al., 2016; Selkoe and Hardy, 2016)) that Aβ plays some kind of significant role in AD, albeit that measures designed to remove it have not led to useful therapeutics (Hardy, 2009; Herrup, 2015; Itzhaki et al., 2016; Karran and Hardy, 2014; Karran et al., 2011). The probable reason for this is simply that it is not the sole actor (though see Note Added in Proof) (Nussbaum et al., 2013), and certainly its interactions with iron salts are central to disease development and loss of cognition (e.g. (Bush, 2003; Bush and Tanzi, 2008; Crapper McLachlan et al., 1991; Fine et al., 2012; Guo et al., 2013; Jomova and Valko, 2011; Kell, 2009, 2010; Kell and Pretorius, 2015b; Malecki and Connor, 2002; Pretorius et al., 2016a; Smith et al., 1997; Smith et al., 2010; Valko et al., 2016)). 'Iron' interacts with fibrinogen too (Nielsen and Jacobsen, 2016; Pretorius et al., 2013, 2014a; Pretorius and Kell, 2014), as does ferritin (Okada et al., 2015). Here we rehearse and develop the additional idea that it is the interactions of Aβ with fibrin(ogen), leading to amyloid fibril formation, that may provide a significant contribution to the neurodegeneration.

An important starting recognition (Cortes-Canteli and Strickland, 2009) is that plasma fibrinogen levels are raised in AD (Davalos and Akassoglou, 2012; Lee et al., 2007; Marioni et al., 2009; Noguchi et al., 2014; van Oijen et al., 2005; Xu et al., 2008), as is coagulability (Gupta et al., 2005; Kell and Pretorius, 2015b). The extent of fibrin deposition reflects the plasma fibrinogen level as it is modified by genetic or pharmacological means (Cortes-Canteli and Strickland, 2009). Fibrinogen is also accumulated in AD plaques (Paul et al., 2007; Ryu and McLarnon, 2009), and this can promote neurodegeneration (Cortes-Canteli et al., 2015).

As well as its general intra- and extra-cellular deposition, a common pathology in AD patients is the deposition of Aβ in the walls of capillaries, arteries, and arterioles. This is known as cerebral amyloid angiopathy (CAA) (Vinters, 1987). Strickland and colleagues next showed (Cortes-Canteli et al., 2010), both *in vitro* and *in vivo*, that fibrin clots formed in the presence of Aβ were structurally abnormal and resistant to degradation, and that lowering fibrinogen improved cognitive function (in mice). (It is also of interest that Aβ promotes the binding of tissue plasminogen activator, which recognises cross-beta sheets (Kranenburg et al., 2002; Longstaff and Kolev, 2015)). Thioflavin S (like thioflavin T, below) is a stain for amyloid fibrils based on their high β-sheet content (Bussière et al., 2004; Ly et al., 2011; Sun et al., 2002). Immunological staining of fibrinogen and thioflavin S staining of (presumed) Aβ showed colocalisation (Cortes-Canteli et al., 2010, 2012), though of course this would not have distinguished whether the fibrin too had adopted a β-sheet form.

Strickland and colleagues next showed (Ahn et al., 2010) that Aβ specifically interacts with fibrinogen (K_d ~ 26 nM), that the binding site is located near the C terminus of the fibrinogen β-chain, and that the binding causes fibrinogen to oligomerise (albeit not to standard fibrin fibres) and to deposit. Although the Aβ will bind to preformed clots, only when it is added before clotting does it produce thinner fibres in tighter networks (Zamolodchikov and Strickland, 2012); it also attenuates plasminogen binding (again consistent with the idea that it induces a structural change in the fibrinogen).

As is well known, the *apoE4* allele is associated with a greater risk of AD; brains from AD cases homozygous for the APOE ε4 allele showed increased deposition of fibrin(ogen), especially in CAA- and Aβ-positive blood vessels (Hultman et al., 2013), fully consistent with the role of this process in cognitive decline. Similarly, pharmacological inhibition with a small molecule called Ru-505 of the fibrinogen-Aβ interaction both altered the clot morphology and arrested cognitive decline (Ahn et al., 2014), implying the potential value of this target (which is also susceptible to enzymatic degradation (Bhattacharjee and Bhattacharyya, 2015)). Overall, the case for an important role of fibrin(ogen)'s interaction with Aβ as part of the aetiology of AD seems very well made. For our purposes, there are two chief questions: (i) what is the extent to which the fibrin adopts an amyloid form when in complex with Aβ?, and (ii) is it more the fibrinogen that precipitates the Aβ or the Aβ that precipitates the fibrinogen?

8. Small molecules that affect the nature of blood clotting and fibrin fibres *in vitro*

The effects of small molecules (both those produced endogenously and introduced drugs) on the coagulation system represent a vast field, and arguably warrant a review of their own, since molecules binding to the normal forms may be expected to inhibit toxic amyloidogenesis (Alavez et al., 2011; Doig and Derreumaux, 2015; Ehrnhoefer et al., 2008; Gavrin et al., 2012; Härd and Lendel, 2012; Hawkes et al., 2009; Hayne et al., 2014; Hirohata et al., 2007; Inbar and Yang, 2006; Jameson et al., 2012; LeVine et al., 2009; Patel et al., 2015; Prade et al., 2016; Ryan et al., 2012; Sarkar et al., 2015; Stempler et al., 2011; Woods et al., 2011) and hence disease (Ahn et al., 2014; Ankarcrona et al., 2016; Flemming, 2014; Hanaki et al., 2016; Jiao et al., 2015; McKoy et al., 2012). However, we here briefly mention a few well-known molecules to illustrate how sensitive fibrin fibre morphology can be to their presence. Various endogenous (inflammatory) molecules, including stress hormones (including the hypothalamic-pituitary-adrenal axis activity) (Austin et al., 2013; von Känel, 2015), activate both the coagulation and fibrinolysis system resulting in net hypercoagulability. It is also well-known that the inflammatory marker 'iron' may cause hypercoagulation in iron-overload diseases (Borgna-Pignatti and Gamberini, 2011; Shah et al., 2015). We have reviewed in detail the effects of increased (endogenous) 'iron', including its effects on the coagulation system (Kell, 2009; Kell and Pretorius, 2015b; Pretorius et al., 2013, 2014a; Pretorius and Kell, 2014). Many drugs introduced into the human body are known to influence the coagulation system; for a comprehensive list of the effects of various drugs on coagulation see (Undas and Ariëns, 2011). The most well-known effect of various drugs on hypercoagulation is thrombotic microangiopathy, which is a pathology that results in thrombosis in capillaries and arterioles, due to an endothelial injury (Reese et al., 2015; Rosove, 2014). Venous thromboembolism, is also a well-known result of the use of oral contraceptives (ESHRE CAPRIWorkshop Group, 2013; O'Brien, 2014).

The above-mentioned molecules and others have direct effects on the fibrin fibre structure and packaging; these include molecules like S-nitrosoglutathione (Bateman et al., 2012), iron and CO

(Nielsen and Jacobsen, 2016; Nielsen and Pretorius, 2014a, 2014b; Nielsen et al., 2015), as well as oestrogen (Swanepoel et al., 2014). We have shown that addition of unliganded iron salts to fibrinogen, to healthy plasma, and/or to whole blood, causes pathological fibrin formation (Lipinski and Pretorius, 2012; Lipinski et al., 2012a, 2012b); however, the addition of various iron chelators to this plasma (Kell and Pretorius, 2015b; Pretorius et al., 2013) results in a return of fibrin fibre structure to become similar to that of healthy fibrin. We also showed that adding chelators to blood/and or plasma from individuals with iron overload (Bester et al., 2013; Pretorius et al., 2014a; Pretorius and Kell, 2014) similarly resulted in the return of the pathologic fibrin structure to that resembling healthy fibrin packaging. See Fig 10, where Fig 10A shows the fibrin fibre structure of an individual with hereditary hemochromatosis and Fig 10 B when the chelators desferal (deferoxamine) is added to plasma of this patient.

9. Induction of amyloidogenic clotting by added LPS (endotoxin)

The very potent bacterial inflammagen, lipopolysaccharide (LPS) is well known to cause cytokine activation, and this can cause hypercoagulation (Chu et al., 2001, 2003); this has been referred to as endotoxin-mediated hypercoagulation (Slotta et al., 2008). One mechanism of activation by LPS of the coagulation pathway is via tissue factor (TF) upregulation (Koch et al., 2009; Monroe and Key, 2007). Previously, it was found that LPS from *Escherichia coli* (100 ng mL^{-1}) activated the coagulation system when added to whole blood, via a complement- and CD14-dependent up-regulation of TF, leading to prothrombin activation and hyper-coagulation (Landsem et al., 2015). Recently, we also found that really minute levels of LPS (0.2 $ng.L^{-1}$, representing a molar ratio to fibrinogen of 1 in 10^8) might bind directly to circulating plasma proteins (when added to plasma from healthy individuals), and also to pure fibrinogen, and that this (rapid) binding might also cause pathological changes in the coagulation process (Pretorius et al., 2016b, 2016c). In our hands, the binding was virtually instantaneous and we confirmed the direct binding of LPS to pure fibrinogen using isothermal calorimetry. It was clear from thioflavin T measurements that LPS could massively affect the formation of β-sheets during fibrin packaging. Only a limited number of autocatalytic mechanisms can admit this, that which we favour (see below) being essentially a very rapid form of amyloidogenesis and autocatalytic structural rearrangement to a β-rich conformation.

10. Anomalous blood clotting involves genuine amyloid formation

What had been determined earlier, and the same was true for changes in erythrocyte morphology (Pretorius et al., 2014a, 2016d; Pretorius and Kell, 2014) and see above, is that small molecules and the presence of various disease states could have massive effects on the morphology of fibrin as judged by (i) its distribution of fibre diameters and (ii) the formation of what we referred to as 'dense matted deposits', in which the fibres were typically much smaller than the normal (whose median ~ 85 nm). What we recently discovered (Pretorius et al., 2016b, 2016c) is that this was actually accompanied by genuine amyloid formation.

As part of a lengthy series on the role of true dormancy in bacterial physiology (e.g. (Kaprelyants et al., 1993; Kaprelyants and Kell, 1992, 1993; Mukamolova et al., 1998, 2002a, 2002b, 2003, 2006; Votyakova et al., 1994)), we have recently come to recognise that a dormant blood microbiome is a significant contributor to a great many chronic, inflammatory diseases, not least by shedding highly inflammatory molecules such as lipopolysaccharide (LPS) (Kell et al., 2015; Kell and Pretorius, 2015a; Potgieter et al., 2015). This led us to assess (Pretorius et al., 2016b, 2016c) whether LPS had any effects on blood clotting directly.

As mentioned, it transpired (Pretorius et al., 2016b, 2016c) that quite miniscule concentrations (amounting to fewer than 1 molecule of freshly added LPS per 10^8 molecules of fibrinogen!) had a massive effect on fibrinogen polymerisation to fibrin, including the production of (in many cases) the thinner fibres and 'dense matter deposits' seen in so many diseases. In particular, the use of the amyloid-detecting dye thioflavine T (Biancalana and Koide, 2010; Freire et al., 2014; Groenning, 2010; Krebs et al., 2005; Kuznetsova et al., 2016; LeVine, 1997, 1999; Lindberg et al., 2015; Picken and Herrera, 2012; Sulatskaya et al., 2011, 2012; Wu et al., 2009) revealed a massive conversion of fibrin to a β-sheet-rich form.

11. The extent of amplification of protein transitions by LPS can be mimicked by liquid crystals

As phrased by Maji and colleagues (Maji et al., 2009), repeating motifs can translate a rather non-specific interaction into a specific one through cooperativity. This process can nowadays be observed directly (Pinotsi et al., 2016), and amounts to potentially quite a massive amplification. In the example of our own mentioned above (Pretorius et al., 2016b, 2016c), with LPS freshly added to whole blood, platelet-poor plasma or fibrinogen solutions, the ratio of LPS:fibrinogen at which the LPS could induce amyloidogenesis was ~1 in 10^8; this represents a truly massive amplification (see also (Galant et al., 2016)), and serves to help explain how very small numbers of bacteria secreting comparatively small amounts of LPS (albeit of potentially high concentration locally) can exert such a massive inflammagenic effect.

Interestingly, Lin and colleagues also showed that similarly tiny

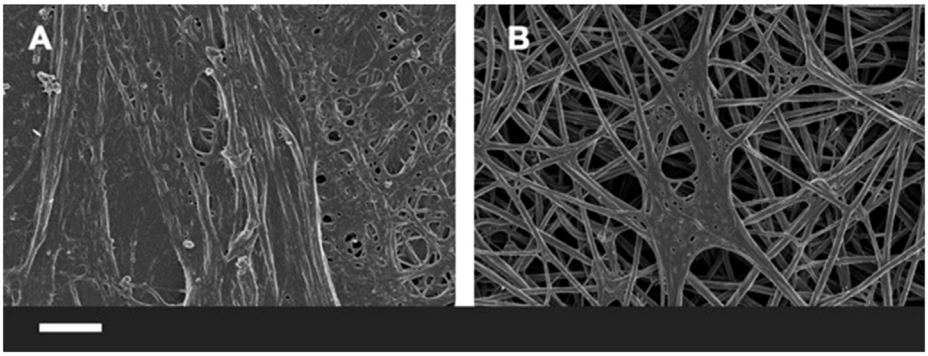

Fig. 10. A) Fibrin fibre structure of an individual with hereditary hemochromatosis; **B)** when desferal (deferoxamine) is added to plasma of this patient. Scale bar: 1 μm.

concentrations of LPS (less than 1 ng.L^{-1}) could also affect the cooperative conformation of millions of molecules in microdroplets of nematic liquid crystals ((Lin et al., 2011), and see (Miller and Abbott, 2013)). The same was true for molecular mimics of LPS (Carter et al., 2015). Indeed, different liquid crystals can also be used as 'biosensors' (Lowe and Abbott, 2012) to detect β-amyloid formation (Sadati et al., 2015), protein-LPS interactions (Das et al., 2015) and microvesicles (Tan et al., 2014).

12. Chronic infection and amyloidogenesis

As phrased by Michael Hann (Hann, 2011), 'unknown knowns' "… are those things that are known but have become unknown, either because we have never learnt them, or forgotten about them, or more dangerously chosen to ignore". Thus, in 1967, Kelényi could write "Development of new therapeutical measures in chronic infections has sharply reduced the incidence of secondary amyloidosis". In other words, the fact that chronic infection could induce amyloidosis was then so well known that it barely merited discussion! The same is true in comparable works of that era (e.g. (Hobbs and Morgan, 1963)). Obviously it has since then been somewhat forgotten, despite the overwhelming evidence (Hill and Lukiw, 2015; Itzhaki et al., 2016) for a microbial component to AD, and to amyloidogenesis more generally (Ebert and Nagar, 2008). Recently (notwithstanding some caveats (Salter et al., 2014)) the role of dormant or latent microbes in chronic, inflammatory diseases more generally has come to the fore (e.g. (Aagaard et al., 2014; Domingue, 2010; Domingue and Woody, 1997; Hieken et al., 2016; Itzhaki et al., 2016; Kell et al., 2015; Kell and Pretorius, 2015a; Mangin et al., 2014; Mattman, 2001; Nicolson and Haier, 2009, 2010; Potgieter et al., 2015; Proal et al., 2009, 2011, 2013, 2014; Urbaniak et al., 2014; Woolard and Frelinger, 2008)), and it is appropriate to recognise this and older literature (e.g. (Billings, 1915; Price, 1923)), some of which is still being rediscovered. Thus, *Chlamydia pneumoniae* induces Alzheimer-like amyloid plaques in the brains of BALB/c mice (Little et al., 2004), while amyloid can also be induced by herpes simplex virus (Wozniak et al., 2007) and *Borrelia* (Miklossy, 2008, 2011; Miklossy et al., 2006). In the present context it is of particular interest that LPS can induce the conversion of prion protein to its amyloidogenic form (provided the LPS concentration remains above its critical micelle concentration (CMC)) (Saleem et al., 2014), and it can do this substoichiometrically. The natural bacterial production of amyloids themselves has also been reviewed (Blanco et al., 2012; Taylor and Matthews, 2015; Van Gerven et al., 2015; Zhou et al., 2012).

13. Serum amyloid A

In a similar vein, 'serum amyloid A' (Benditt et al., 1971) describes a heterogeneous family of apolipoproteins (Sipe, 1999) (and variants (Nedelkov et al., 2005)) that form amyloid fibrils in the blood, typically in response to inflammation or infection (Malle and De Beer, 1996; Röcken and Shakespeare, 2002; Sipe, 2000), binding retinol in the process (Derebe et al., 2014). To this end, this rather understudied series of proteins may provide very useful biomarkers for chronic infection/sepsis, for which it is in fact a well-established (and potent) biomarker (e.g. (Arnon et al., 2007; Bozinovski et al., 2008; Çetinkaya et al., 2009; Cicarelli et al., 2008; Derebe et al., 2014; Ebert and Nagar, 2008; Falsey et al., 2001; Lannergård et al., 2008, 2009; Malle and De Beer, 1996; Obici et al., 2005; Pizzini et al., 2000; Sipe, 2000; Urieli-Shoval et al., 2000; Yamada, 1999; Yuan et al., 2013a)). Interestingly, and in a manner akin to that of prions, it is able to catalyse its own α-to-β-type conformational transitions (e.g. (Liu et al., 2007; Lundmark et al., 2002, 2005; Murakami et al., 2015; Murakami et al., 2014; Tasaki et al., 2010; Westermark et al., 2009)), although the kinetics are rather sluggish compared to those of blood clotting. In a similar vein, amyloid deposition in the kidney (Dember, 2006; von Hutten et al., 2009) may account for the proteinuria seen in diseases such as pre-eclampsia (Kell and Kenny, 2016).

14. Sequelae of amyloidogenesis

While the focus of this review is on amyloidogenesis *per se*, we should recognise its sequelae at various levels. Pertinent to the blood system is the fact that amyloid can induce gross morphological changes in erythrocytes, leading to their suicidal death ('eryptosis') (Nicolay et al., 2007). Indeed, our own observations show that major morphological changes in erythrocytes are a regular accompaniment to the chronic inflammatory diseases that we are discussing (e.g. (Bester et al., 2013, 2015; Pretorius et al., 2015, 2014a, 2014b; Pretorius and Kell, 2014; Pretorius and Lipinski, 2013b, 2013c; Pretorius et al., 2016d)), and these sequelae can include eryptosis (Pretorius et al., 2014c). Eryptosis is characterized by scrambling of the cell membrane with subsequent exposure of phosphatidylserine (PS) at the cell surface (e.g. (Lang et al., 2012; Qadri et al., 2016)), and is essentially a form of apoptotic cell death (Lang et al., 2015a). Interestingly (and perhaps surprisingly) this eryptosis involves the cyclin-dependent kinase CDK4 (Lang et al., 2015b).

As indicated above, many human diseases are known to be associated with misfolded or amyloid-type proteins (Chiti and Dobson, 2006; Herczenik and Gebbink, 2008; Knowles et al., 2014; Moreno-Gonzalez and Soto, 2011; Olanow and Brundin, 2013; Pawlicki et al., 2008; Rambaran and Serpell, 2008; Tipping et al., 2015; Westermark and Westermark, 2011; Zhang et al., 2014), and the cytotoxicity of amyloid fibrils is very well established (e.g. (Ahmed et al., 2010; Airoldi et al., 2011; Bester et al., 2015; Cao et al., 2013; Fernández, 2014; Hefti et al., 2013; Kayed et al., 2003; Kayed and Lasagna-Reeves, 2013; Konarkowska et al., 2006; Liu et al., 2011; Lorenzo et al., 1994; Marzban et al., 2003; Meier et al., 2006; Meyer-Luehmann et al., 2008; Minter et al., 2016; Miranda et al., 2000; Rival et al., 2009; Sengupta et al., 2016)). We note, however, that although it is the larger fibrils that are observable ultramicroscopically, there is evidence that it is the smaller ones that are the more cytotoxic (Aitken et al., 2010; Baglioni et al., 2006; Bucciantini et al., 2002; Dobson, 2013; Fändrich, 2012; Glabe, 2006; Göransson et al., 2012; Haass and Selkoe, 2007; Janson et al., 1999; Kayed et al., 2003; Konarkowska et al., 2006; Meier et al., 2006; Pillay and Govender, 2013; Stefani, 2012; Trikha and Jeremic, 2013; Uversky, 2010; Xue et al., 2009, 2010; Zhang et al., 2014). As to the mechanism of cytotoxicity, membrane permeabilisation (followed by apoptosis) is certainly one (Cao et al., 2013; Engel et al., 2008; Janson et al., 1999; Nanga et al., 2011).

15. Possible treatments for coagulopathies in the light of their role in amyloidogenesis

Recognising that 'dense matted deposits' are actually amyloid encourages one to access the literature designed to stop or reverse amyloidogenesis in other fields such as Alzheimer's disease (e.g. (Ahn et al., 2014; Bieschke, 2013; Brumshtein et al., 2015; Cheng et al., 2012, 2013; Doig and Derreumaux, 2015; Eisele et al., 2015; Estrada et al., 2006; Flemming, 2014; Hanaki et al., 2016; Hawkes et al., 2009; Jucker and Walker, 2013; López et al., 2012; Murakami, 2014; Stamford and Strickland, 2013), and see also (Cegelski et al., 2009; Cheng et al., 2016; Evans et al., 2015; Klein and Hultgren, 2015)) or for transthyretin (Ankarcrona et al., 2016; Galant et al., 2016), and thus it will be of interest to assess candidate anti-amyloidogenic molecules in the blood system, where it is

not, at least, necessary for them to cross the blood-brain barrier (see (Kell, 2015; Kell et al., 2011, 2013; Kell and Oliver, 2014)).

In a complementary vein, if (anomalous) fibrin clot formation is significant in AD one might suppose that inhibiting it might be of value, and it is (Ahn et al., 2014). One might also expect that anticoagulant therapies might show benefit, and there are some significant hints that this too might indeed be the case (Barber et al., 2004; Murthy et al., 2009; Ratner et al., 1972; Walsh, 1996; Walsh et al., 1978), to the extent that this would seem to be well worth exploring properly. The success of the anticoagulant thrombomodulin in sepsis/septic shock (Eguchi et al., 2014; Hayakawa et al., 2016; Levi, 2015; Levi and Van Der Poll, 2013b; Mimuro et al., 2013; Saito et al., 2007; Shirahata et al., 2014; Vincent et al., 2013; Yamakawa et al., 2015; Yoshimura et al., 2015) also implies an important role of coagulopathies there.

Since the levels of fibrinogen themselves seem to correlate with a propensity for AD (see above), and indeed for hypertension (Bembde, 2012; Haenni and Lithell, 1996; Letcher et al., 1981; Shankar et al., 2006), lowering them to more appropriate levels (by means other than by converting them to amyloid forms of fibrin!) would seem to be a desirable aim in itself.

16. Quo vadis? – systems strategies

We have summarised much of the evidence to the effect that under some circumstances the fibrin fibres formed by fibrinogen polymerisation are in fact amyloid in character (Fig 11). This opens up the field to testing this under the many different disease circumstances where this might be suspected, whether as a diagnostic or a prognostic. Easy predictions are that the clots seen after stroke and in any other hypercoagulable conditions will be amyloid and thus stainable with thioflavin T or amyloid-selective dyes (noting the need for suitable controls and caveats (Coelho-Cerqueira et al., 2014; Hudson et al., 2009; Wong et al., 2016)). The many established methods for β-amyloid detection include spectroscopies (e.g. X-rays (Guilbaud and Saiani, 2011; Sawyer and Gras, 2013; Spencer et al., 2015), NMR (Colvin et al., 2015; Karamanos et al., 2015; Su et al., 2015; Tycko, 2011), mass (Riba et al., 2015; Young et al., 2014, 2015), circular dichroism (Etienne et al., 2007; Howie and Brewer, 2009), neutron (Valincius et al., 2008), vibrational (Dasari et al., 2011; Middleton et al., 2012)) and microscopies (including appropriate stains (Fig 11 and above)) will be of value in detection. SEM and TEM (Iadanza et al., 2016) were discussed above, but there is a clear role too for AFM (Volpatti et al., 2013). Similarly, a plethora of small molecule studies will clearly be of value in seeking to modulate such amyloid formation. As is common in modern biology, strategies for pharmacological inhibition are usually done piecemeal on the basis of specific hypotheses about individual targets. Clearly this must change (Kell, 2013). We have highlighted several 'non-traditional' targets here (e.g. iron metabolism, blood clotting, fibrinogen-Aβ interactions, anti-amyloids) but they have only been studied singly.

From a network or systems pharmacology perspective (e.g. (Berger and Iyengar, 2009; Cucurull-Sanchez et al., 2012; Hopkins, 2008; Kell and Goodacre, 2014; van der Graaf and Benson, 2011)), we either need polypharmacology (one drug, multiple targets, e.g. (Achenbach et al., 2011; Anighoro et al., 2014; Hu and Bajorath, 2010; Kell, 2013; Kell and Goodacre, 2014; Kell and Oliver, 2014; Mestres and Gregori-Puigjané, 2009; Peters, 2013; Reddy and Zhang, 2013; Weinreb et al., 2011, 2012, 2010; Xie et al., 2012). or suitably combined cocktails of individual drugs (e.g. (Borisy et al., 2003; Lehár et al., 2007, 2008; Small et al., 2011; Zimmermann et al., 2007)). Armed with these, and based on established mechanisms of action that involve fibrin(ogen), we may strongly hope to delay the progression of amyloidogenic diseases in our ageing populations.

In a related vein, we would be remiss not to recognise that an understanding of how small trigger events can effect massive conformational changes in designed proteins has potentially massive benefits for synthetic biotechnology (Currin et al., 2015; Li et al., 2014), including self-assembling systems (Boothroyd et al., 2014; Elsawy et al., 2016; Hickling et al., 2014). Nakano and colleagues provide a very nice biomaterials example with barnacle

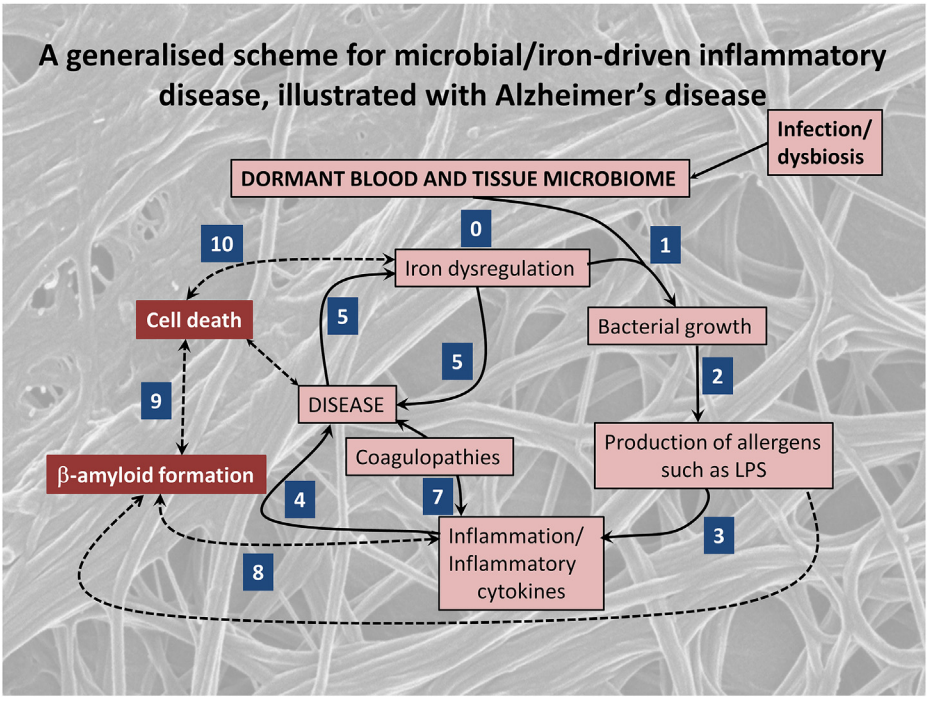

Fig. 11. An elementary systems biology model of how iron dysregulation can stimulate dormant bacterial growth that can in turn lead to antigen production (e.g. of LPS) that can then trigger inflammation, leading to β-amyloid formation in fibrin and ultimately to cell death.

glue (Nakano and Kamino, 2015).

Overall, the crux of the review is that we have indicated that many more proteins than perhaps currently recognised, and in particular fibrin(ogen), can form genuine amyloid structures that are likely to be significant in toxicity and disease; clarifying the link between their essential molecular structure/conformation and their disease-causing potential is now key, and the fields of blood clotting and amloidogenesis can learn much from each other to mutual advantage.

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Note added in proof

Very recently, Sevigny et al. (2016) have shown that aducanumab may clear Abeta plaques in a mouse model, with addendant improvement in cognitive function.

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