**Introduction**

Peyronie’s disease (PD) is a fibrotic penile connective tissue disorder, localized on the tunica albuginea, a connective tissue sheath surrounding the erectile tissue. Currently, it is an incurable and sexually debilitating male affliction, named after the French surgeon Francois Gigot de Lapeyronie (1678-1747). In 1743, during his service as the first-surgeon of King Louis XV, he described an induration of the penis resulting in curvature. Ever since, it has been a disease underestimated in both prevalence and impact. Since the first description of its natural history by Williams & Thomas in 1970, it has led clinicians to adopt a rather conservative treatment approach. In the case series of 21 patients reported in this first study, none had reported worsening [1]. However, by 1990 it was clear that spontaneous resolution was not as frequent as previously thought. Gelbard et al. [2] revealed that only 13% of patients had complete disappearance of the plaque. Moreover, 40% reported significant worsening and more than three-quarters reported a negative impact on their psychological status. Similar numbers were reported by Mulhall et al. in 2006 [3] and Kadioglu et al. [4] in 2007. Prevalence ranges from 1-3% across Western Europe, but screening studies have shown that this might only be the tip of the iceberg. The prevalence increases with age and pre-existing ED, up to 9% [5,6].

PD is defined by the formation of disarranged collagen and elastin depositions, leading to a fibrous plaque. First, a painful stage of inflammation ensues (acute phase). During this initial phase, the plaque progressively retracts, and sometimes calcifies and ossifies completely. Second, a stable, permanent, more-often-than-not painless deformity is left behind (the chronic stage) [7]. This may present as a curvature or a complex deformity resulting in coital failure. It is frequently accompanied by severe and difficult-to-treat ED in 20-54% of the cases [8,9].

Currently, the available treatment options recommended by international guidelines are limited to either surgery or local injection of collagenase or interferon α-2B [10]. A recent systematic review by Russo et al. [11] shows that only collagenase and interferon injection therapy are accompanied by sufficient levels of evidence to recommend usage in clinical practice. Collagenase is administered to break down the rigid extracellular matrix, mainly consisting of collagens. The mechanism of action of interferon has been investigated in a study in 1991 by Duncan et al., where the authors showed an anti-fibrotic effect on cultured fibroblasts. [12] Surgery is an effective solution, yet it can lead to glandular hypo-esthesia and a high risk of worsening/new-onset of ED. Additionally, intralesional injections can be paired with side-effects (pain, corporal rupture and allergic reaction) and only cause a limited improvement in curvature (up to 30%) [11]. Both interventions aim to improve the ability to resume sexual intercourse by correcting the final deformity in the chronic phase of the disease, not offering a cure for the underlying disease. They do not focus on the underlying driving pathophysiological process leading to PD. The use of oral and other intralesional therapies is not supported by acceptable levels of evidence to warrant their use in a clinical setting [11]. There is an unmet need for improved therapeutic options for PD patients, especially in the early stages. It could lower the cost of treatment and number of patients needing surgery.

Due to surgery being able to correct the most pressing physical deformity, along with the apparent underestimation of its prevalence, the general motivation for etiological and pathophysiological studies on a cellular and molecular level have been relatively scarce. However, in the past few years there has been an increased interest for basic research involving PD, including the development of an animal model (first in 1997 by El-Sakka et al. [13,14]), *in vitro* cell culture models [15–20] and extrapolation of what is known from the pathophysiology of other fibrotic diseases, such as cardiovascular, kidney, liver fibrosis and fibrosis associated with burn wounds [21–24].

Even though PD has been known to exist for over 250 years, little advances have been made toward unravelling the exact aetiology and pathophysiology of the disease. The most widely accepted hypothesis remains that of Devine et al. [25] made in 1997, involving repetitive trauma to the erect penis during intercourse. This is consistent with the fact that repetitive arduous muscle loading can lead to a process of microinjury and repair, but also to inappropriate healing, fibrosis and even calcification [26]. Several overlapping actions occur in a temporal fashion; (micro)traumata, fibrin deposition (stabilised by transglutaminase-mediated cross-linking to fibronectin), inflammation with attraction of macrophages and fibroblasts, stimulation of the release of cytokines, especially transforming growth factor beta-1 (TGF-β1), myofibroblast (MFB) formation, extracellular matrix (ECM) production, contraction and stabilization, and finally calcification. The interrelation of the various stages and which key signals initiate these processes are poorly defined. Due to its relative sparsity and uncommon need for resection of plaque tissue, especially in the active phase of the disease, the human phenotype has been widely understudied. Very few *in vitro* models for PD exist. Most have been based on the isolation of PD fibroblasts from excised plaques obtained from patients with PD. These patches can be compared to fibroblast from non-affected areas of the tunica albuginea (TA) of PD patients or TA fibroblasts in healthy patients. The outcome measures in these studies had been set as the production of extracellular matrix in response to stimulation by TGF-β1 and most importantly the transformation of fibroblasts into myofibroblasts [18–20,27]. In this review we aim to provide an overview of the pathways and pro-fibrotic mechanisms potentially involved in PD. First, we will describe what is currently known regarding the pathophysiology of PD. Second, we will discuss what this means for the development of new medical treatments for PD.

***Fibrosis***

The pathology of fibrosis embodies a spectrum of disorders encompassing many different organs (i.e. lung, kidney, liver, heart and skin fibrosis). Its main characterisation is the excess accumulation of ECM in response to chronic inflammation. Fibrosis can be considered as an abnormal (or excessive) wound healing response and occurs often as the final pathological outcome of chronic tissue injury. While initially reversible, the chronic nature of the occurring inflammation drives it towards a permanent scar formation which leads to organ dysfunction and/or failure, as evident in end-stage fibrotic kidney, heart, liver and lung failure [28–36]. Fibrosis and extracellular matrix imbalance are an abundant feature of autoimmune processes, tumoral invasion and metastasis, chronic graft rejection and progressive myopathies [28–30]. More often than not, the precise trigger for the fibrotic process is unknown, but can be attributed to one of the following aetiologies; persisting infections, exposure to toxins, genetic disorders, chronic autoimmune inflammation, metabolic syndrome, or hypertension [28]. Notwithstanding the aetiology or tissue type involved, all fibrotic diseases have a common feature, represented by a specialized cell type called myofibroblasts (MFBs). Their unique features include increased proliferation rate, ECM-production, contractile ability, migration in response to chemotactic stimuli, contributing to the inflammatory response and angiogenesis in a paracrine way [37]. Despite MFB having a key pathogenic role in fibrotic disease, there is a notable lack in treatment strategies to specifically target this process, although myofibroblast elimination has been suggested [18,38,39]. However, myofibroblasts and other inflammatory cells do not exist in a vacuum and the environment can significantly impact their response. The role of the ECM as being both a conductor and part of the fibrotic orchestra is becoming increasingly recognized [40]. More than just a scaffold for cells, it can has a prominent function in initiating and maintaining the profibrotic milieu [41] and hereby provides a novel target for pharmacological intervention. This complex interconnectivity between ECM, myofibroblasts and macrophages was reviewed recently by Pakshir & Hinz [40]. In short, the ECM initiates inflammation through providing a scaffold for fibrin accumulation and accumulation of inflammatory cells (e.g. macrophages), activating various precursors into myofibroblasts (by transduction of mechanical stress) and “unwrapping” of latent TGF- β1 stores [42]. Integration of fibrillary proteins (e.g. collagens I-III-V-XI, elastin, fibronectin), glycoproteins (e.g. collagens IV-VI-VIII-XIV, tenascin, hyaluronan) and matricellular proteins (CCN2, periostin, osteopontin, osteonectin) causes stiffening and remodelling of the ECM. Which further enhances myofibroblast activation. Moreover, these fibrils provide highways for attraction of fresh pro-fibrotic factors (e.g. TGF- β1) as myofibroblasts “tug” macrophages into their vicinity. The exact mechanisms driving fibrosis have been reviewed extensively elsewhere by Cannito et al. and Wynn et al. [28,37].

***Role of the innate immunity***

During an acute insult to the tissue (for example, trauma, infection, toxins), an attempt to restore homeostasis is initiated by recruiting cells of the innate immunity (macrophages, neutrophils and antigen-presenting dendritic cells) [37]. The initiating trigger for this complex response can be different depending on the type of insult. When the endothelium is damaged, circulating platelets release (I) coagulation factors for haemostasis (activation of fibrin) and (II) growth factors, such as platelet-derived growth factor (PDGF), a potent chemoattractant for inflammatory cells, and TGF-β1, which stimulates ECM production by resident fibroblasts [27,43,44]. Aside from its ubiquity in the coagulation cascade, thrombin also activates the chemokine (C-C motif) ligand 2 (CCL2). Myeloid cells (later; macrophages) migrate from the bone marrow to the site of injury by responding to the CCL2 gradient. Together with neutrophils these cells are important for the initial wound-healing response. However, they release a wide array of toxic mediators (reactive oxygen and nitrogen species) [45] which exacerbate the tissue-damaging if they are not removed timely. Other triggers include pathogen-associated molecular patterns (PAMPs; invading microorganisms) or damage-associated molecular patterns (DAMPs). DAMPs are released from dead cells, proliferating neutrophils, macrophages, lymphocytes, NK cells, mesenchymal stem cells, as well as resident cells (mainly fibroblasts, epithelial and endothelial cells, and adult stem cells) [28–30]. Both recruited and resident macrophages can differentiate and undergo key functional changes in response to the local tissue environment containing PAMPs, DAMPs, ROS, GFs and cytokines. Pro-inflammatory macrophages can exhibit a strong microbiocidal and tumoricidal activity through high levels of expression of autocrine/paracrine cytokines such as IL-1b, TNFα and IL-6 [46]. Macrophages also have an important role in activation of the MFBs through the release of TGF-β1 [46]. Furthermore, they show increased production of reactive nitrogen and oxygen species, and stimulate Th1 response. The drive towards this phenotype is mainly characterised by IFNy and TLR-activated interferon regulatory factor (IRF)/signal transducer and activator of transcription-1 (STAT1) signalling [46,47].

***Myofibroblasts: a unique duality***

Myofibroblasts are possibly the most unique, and the most controversial cells in the wound healing process [48]. They can actively regulate the ECM, while at the same time possessing a cytoskeletal contractile apparatus like smooth muscle cells. MFB represent a heterogeneous group of α-smooth muscle actin (α-SMA)-positive cells, originating mainly from fibroblasts, but also from a plethora of other sources [28–36]. Fibroblasts (and other cell types) undergo a phenotypical switch following acute tissue injury which represents a crucial step in the restoration of tissue integrity. During tissue injury, the most important myofibroblast progenitor is difficult to determine. It can vary between types of injury and tissue and includes either (1) epithelial/endothelial cells, which can be subjected to respectively epithelial- or endothelial-to-mesenchymal transition (EMT or EndoMT), (2) local pool of tissue-resident FBs, (3) circulating fibrocytes (derived from bone marrow), (4) local mesenchymal stem cell niche or (5) smooth muscle cells [44,49]. Once wound healing has been completed, MFB are eliminated mainly through apoptosis, although reversal to a quiescent state has been proposed 52. However, under conditions of chronic tissue injury or dysregulated wound healing, their activity becomes excessive, with the cells becoming resistant to apoptosis, which allows them to contribute significantly in tissue fibrosis and ultimately dysfunction [48,50].

A phenotypical switch of local cells to MFB is indicated by the production of the myofibroblast marker a-SMA, and ECM-components such as collagens (mostly type I and III), laminin, and fibronectin, a process that is mainly driven by TGF-β1 [51–54]. There is an apparent association with dysregulation of genes involved in the homeostasis of the ECM and its remodelling. Matrix metalloproteases (MMPs) (which remove excessive fibrillary collagen fibers) and their respective inhibitors, tissue inhibitors of metalloproteases (TIMPs), are examples of such an imbalance, with an inhibition of the former and upregulation of the latter present in fibrotic conditions [51–54]. Release of causative cytokines such as TGF-β1 can either be mediated through the presence of peripheral/resident macrophages or through autocrine/paracrine action of the MFB itself. A role can be highlighted for another mediator causing ECM production and MMP/TIMP imbalance: reactive oxygen species (ROS). These are either produced by damaged parenchymal or epithelial cells, or through cytokine-mediated activation of NAPDH-oxidase isoforms (NOX). Several cells (epithelial, endothelial, macrophages, infiltrating leukocytes) in the pro-fibrogenic environment can contribute to ROS generation through NOX-isoforms. Research has shown that inducible nitric oxide synthase (iNOS) acts as an anti-fibrotic and ROS scavenging mechanism in PD [27,54].

During the progress of fibrosis, the MFB exhibit highly proliferative tendencies due to the pro-fibrotic environment and expression of mitogenic factors by surrounding cells [51–53]. PDGF is the most potent of these mitogenic factors, and a strong chemotactic factor in this setting [29,43,55]. Moreover, PDGF production and the expression of related receptors is sustained by TGF-β1 signalling [29,43,55]. Pro-angiogenic factors are also believed to be essential for delivery of paracrine factors to adjacent endothelial cells, in order to augment the MFB-induced fibrogenic progression. Neo-angiogenesis is driven by hypoxic conditions which trigger an immediate mitochondrial-dependent ROS-mediated activation of the JNK- and ERK-pathways and a delayed, HIF-1α-dependent upregulation and release of VEGF, facilitating a fibrotic response [56].

In summary; there are a few critical concepts for progression of fibrotic disease, which are generally applicable: 1) persistent chronic tissue injury leads to activation of MFB and release of ROS, 2) ongoing recruitment of innate and adaptive immune systems creating a pro-fibrogenic environment, favouring chronic inflammation, 3) inefficient remodelling modulated by tissue hypoxia and subsequent neo-angiogenesis and 4) fibrosis may be potentially reversible by removal of inciting agent or exposure to correct therapy (as evidenced in pre-cirrhotic livers) [32,57].

***Fibrosis in PD***

As previously mentioned, it is hypothesized that microtrauma lead to an inflammatory reaction in the TA. During sexual intercourse, a buckling force is exerted on the penile shaft due to curving of an otherwise straight object. This occurs in presence of a significant axial compressive load, as is the case during repetitive pelvic thrusting [58,59]. The anatomical structure of penile TA consists of two laminated, distinct layers (one longitudinal, the other circular) that fuse to form a median septum. The area of mechanical stress demonstrates a temporary de-lamination of the TA, causing microvascular trauma. Curiously, multiple epidemiological studies investigating the incidence of PD after penile fracture or history of forcefully bending the erect penis as in Taqaandan practice in some Eastern cultures did not show a correlation. This may suggest that there may be several unknown genetic and/or systemic factors at play that cause PD [60,61]. These factors could include oxidative stress, cytokine release, and autoimmunity; however, it is difficult to harmonize this with the idea that a certain effector causes a specific, localized plaque instead of a generalized fibrotic reaction.

This fibrotic process is resolved in normal wound healing by inhibition of fibroblast proliferation and differentiation into MFB, MFB apoptosis, cessation of collagen synthesis, and fibrinolysis and collagen degradation by the MMPs. In renal fibrosis it has been shown that impeding this process causes myofibroblast and fibrin persistence by increased plasminogen activator inhibitor 1 (PAI-1). PAI-1 is a potent inhibitor of fibrinolysis and down-regulator of MMP activity [62]. This was corroborated by Davila et al. [63] where they found a significantly increased mRNA and protein levels of PAI-1 in human PD plaques and PD-derived cell cultures alike. Also, fibrin was found in human and rat plaque tissue, and injection of fibrin into the rat TA caused PD-like plaques with increased TGF-β1, ROS, α-SMA, PAI-1 and iNOS expression [63].

TGF-β1 was discovered to be elevated in PD plaques and subsequently has spurred new *in vitro* and *in vivo* research investigating the pathophysiology of PD. Administration of TGF-β1 to PD-derived or normal TA cells has been the go-to *in vitro* model for over a decade [18,19,64]. Similarly, the most widely used animal model remains injection of TGF-β1 into the rat TA. This causes the development of a fibrotic lesion after 5-6 weeks and histology shows a PD-like plaque. Transforming growth factor proteins are an extensive family of growth factors essential for a diverse set of functions during embryogenesis and adult tissue homeostasis [65]. In its simplest form, TGF-β1 transduces its signal through membrane receptors with serine/threonine kinase activity. This involves binding to TGFβ-RI and TGFβ-RII mediating intracellular signaling through phosphorylation of SMAD2/3 (DNA-binding proteins that recruit transcriptional co-activators or -repressors). This forms a complex together with SMAD4 that can translocate to the nucleus and induce transcription of target genes. A negative feedback loop through SMAD7 functions through the TGFβ-RI by blocking SMAD2/3 polymerisation, thus facilitating degradation by ubiquitination and proteasome action [66]. Non-canonical (SMAD independent) pathways are regulated through small GTPases (mainly RhoA and Cdc42) and leading to activation of MAP kinases such as c-jun-NH2-terminal kinases (JNK), ERK ½ and p38 (29, 105, 164) as well as PI3K. TGF-β1 induced activation of ERK1/2 activates CTGF/CCN2 and type 1 collagen synthesis, whereas JNK, p38 and PI3K/Akt contribute in phenotypical switch of precursors in MFBs [67]. For its pro-fibrotic role, TGF-β1 is secreted by a variety of cells such as macrophages, MFB, endothelial and epithelial cells. When released, it mainly influences recruitment of macrophages, fibroblast to MFB phenotypical switch, proliferation of MFB and stimulating both cell types to release several other fibrogenic cytokines [28–36]. Recent *in vitro* research revealed that PD-derived fibroblasts when stimulated with TGF-β1 not only show an increased expression of fibrillary extracellular matrix proteins such as collagen I, III and elastin, but also of the matricellular protein CTGF/CCN2 [20]. Inhibition of the non-canonical RhoA-signalling by the Rho-inhibitor Y-27632 and simvastatin causes an impaired myofibroblast transformation, as well as attenuated expression of both fibrillary and matricellular proteins [20].

However, the role of the innate immune system and macrophages in the chronic inflammation of PD had not been suggested until recently. In a study by Milenkovic et al. (unpublished data) [68], the investigators compared the transcriptomic content of PD plaque tissue versus control TA (from patients undergoing non-PD related penile surgery) using RNA sequencing. Subsequently, broad clustering of gene sets using gene ontology revealed not only, an expected, high extracellular matrix turn-over, but a strong immunological component as well. Moreover, gene clusters and signatures indicate an important role for DAMP-activated macrophages in maintaining this chronic inflammation. However, caution needs to be taken when interpreting these results. Plaques were taken only from patients in the chronic disease stage, so a certain amount of interpolation is necessary to understand what is happening in the acute inflammatory phase. An updated hypothesis, one that is complementary to the existing model, of the pathophysiology of PD is provided in Fig. 1.Tissue fibrosis can also be driven by oxidative stress and reactive oxygen species (ROS). ROS are produced more prominently by PD-plaque human or rat FBs and trigger lipid peroxidation with subsequent potentiation of TGF-β1 [15,17,69]. This is not only the case in PD, but also in atherosclerosis, diabetes mellitus, hepatic, renal and pulmonary fibrosis [28–36]. Several studies have shown that typical markers of ROS such as xanthine oxidoreductase and heme-oxygenase I increase concomitantly with collagen production. Due to rising ROS levels, there is an elevated expression of iNOS [15,17,69]. Nitric oxide (NO) produced by iNOS interacts with ROS as a protective mechanism and forms peroxynitrite, allegedly impeding fibrotic deformities [69,70]. This is supported by the fact that long term treatment with L-N6-(1-iminoethyl) lysine acetate (L-NIL) increases collagen and ECM deposition in a PD rat model. Interplay between the oxidative and nitric oxide-related pathways is best studied in the corporal smooth muscle cells in aging and diabetic forms of ED [71,72].

A handful of studies have explored mesenchymal stem cells and stromal vascular fraction in the treatment [44,73–78]. This cellular and molecular interrelatedness could explain the increase in stem cell research, owing to their ability to release several immunomodulating factors (a local “drug store”), influencing multiple pathways and cells simultaneously. This goes beyond the scope of this review and has been studied extensively elsewhere [44].

***Genetic factors and gene expression in Peyronie’s Disease***

In the past decades, significant advances have been made toward the understanding of the underlying genetic factors associated with PD [79]. It was initially suggested by Bias et al. [80] in 1982 that there may be a genetic background to PD using a pedigree analysis of three families who had both PD and DD. An autosomal dominant inheritance pattern with incomplete penetrance was suggested. Willscher et al. [81] found that there was increased occurrence of HLA-B7 cross-reacting group in PD patients in comparison to the normal population. However, the roles of HLA loci and antigen expression in the development of PD have been largely debated [82–84]. PD cell culture models have shown chromosomal instability in plaque-derived fibroblasts, but not in fibroblasts taken from adjacent TA, dermis and lymphocytes in men with PD. Somers et al. [85] showed duplication of chromosome 7 and 8 and deletion of chromosome Y. Similarly, Mulhall et al. [86] showed aneuploidy of chromosome 7 and 8, followed by 17 and 18, and finally Y and X chromosomes. As stated before, elevated levels of TGF-β1 have been associated with PD. The precise mechanism for its elevated levels has not been elucidated yet, but it could potentially be explained in part by the existence of heritable single nucleotide polymorphisms. The only SNP that has been associated with PD in a large cohort (111 PD patients vs 100 healthy controls) is the G915C SNP, resulting in the substitution of arginine in proline at position 25 in the TGF-β1 protein [84,87]. Eleven other SNPs that were associated with certain chromosomal loci were found in a genome wide association study of 2,325 patients. Six of these related to the wingless-type MMTV integration site (WNT) signalling pathway [88,89].

Gene expression profile studies between PD-derived lesions and normal TA have also been performed. Using the Clontech and Affymetrix DNA microarray platforms 7 patients with PD and 5 patients with normal TA were examined [90]. Using the Clontech platform, the genes with the highest differential expressions were revealed to be pleiotrophin (*PTN/OSF-1*, a growth factor inducing fibroblast proliferation, osteoblast recruitment and osteogenesis) and monocyte chemotactic precursor protein 1 (*MCP-1*) gene. MCP-1 does not only recruit peripheral blood monocytes but drives the inflammatory cascade as well. Using the Affymetrix platform, mainly genes involved in the fibroblast-myofibroblast differentiation were detected to be overexpressed (fibroblast muscle type tropomyosin, myosin light chain, filamin, smooth muscle alpha actin, desmin), as well as genes responsible for fibroblast attachment and collagen production (cadherin, TGF-β1, and insulin-like growth factor binding protein-6), elastin degradation (elastase IIB24), and the cellular stress response (heat shock protein). The most notable downregulated gene was mothers against decapentaplegic homolog 7 (*SMAD7*). This is likely to have a pro-fibrotic effect in PD, given that SMADs are essential in TGF-β1 signalling. SMAD7 is an important part of the self-regulatory TGF-β1 pathway axis, forming a negative feedback loop [91,92]. Consequently, overexpression of SMAD7 could limit the fibrotic response of PD fibroblasts. Choi et al [66] demonstrated that fibroblasts transfected with SMAD7 have profoundly decreased plasminogen activating inhibitor-1 (PAI1), fibronectin, collagen I and collagen IV relative to empty vector PD plaque-derived fibroblasts.

A recent study by our group using next-generation RNA sequencing revealed a large amount differentially expressed genes. Subsequent gene set enrichment, transcriptional regulation analysis revealed that NF-kB and STAT-signalling could play an important role in the sustained fibrosis of PD. Activation of the NF-kB pathway mainly occurred through TNFα and Toll-like receptor signalling, while STAT-activation was mediated by cytokines and type I/II interferons [68].

***A new era of drug discovery in Peyronie’s disease***

The advent of rapidly evolving genomics and recombinant DNA technology in the 1990s has caused a paradigm shift in the way drugs are being developed [93]. The focus has shifted toward modification of target proteins involved in the pathogenesis of a disease (target-based approach) either by small-molecules or biologicals (therapeutic antibodies) [94]. Screening of small-molecules that can bind to specific pre-determined single molecular target can be carried out in a high-throughput manner. A disadvantage of this single-target based approach remains that the proposed molecular hypotheses may not be relevant to the pathogenesis or progression of the disease. However, prior to this development, drug discovery had been mainly driven by phenotypic assays, mostly unaware of the molecular mechanism of action [93]. Even after turning the major focus of drug discovery toward target-based approaches, only 17 first-in-class molecules were discovered using target-based screening, opposed to 28 first-in-class molecules using phenotypic screening. Therefore, it has been suggested that relative abandonment of the phenotypic approach has led to the current relative lack of success in drug research and development [95]. Additionally, phenotypic screening should be applied to tackle drug discovery in fibrotic diseases [96] as it is more biologically and disease relevant to modulate a certain pathological phenotype opposed to an isolated pathway [97]. Every living organism undergoes injury during its lifetime. Tissue repair is one of the oldest and most redundant evolutionary mechanisms developed to ensure survival. Therefore, acute inflammation, chronic inflammation and tissue injury is a tightly orchestrated symphony of myofibroblasts, macrophages and extracellular matrix [40]. This also means that compensatory pathways for tissue repair are ubiquitous and impairment of one pathway leads to the activation of a flurry of compensatory pathways. Which is likely the reason why only two drugs (nintedanib and pirfenidone) have been FDA/EMA approved for the use in (pulmonary) fibrosis [28].

A major disadvantage of phenotypic screening assays remains that they have a considerably lower throughput than target-based assays [97]. However, a recent publication by Ilg et al. [19] shows the development of a high-throughput *in vitro* phenotypic screening assay designed for PD. The authors use a TGF-β1-based fibroblast-myofibroblast transformation model, where they screened twenty-one molecules previously suggested for treatment of PD. The investigators demonstrated a synergistic antifibrotic effect in vitro and in vivo when combining phosphodiesterase type 5 inhibitors (PDE5is) and selective estrogen receptor modulators (SERMs). Regarding PDE5is, there is a body of preclinical evidence supporting its antifibrotic properties. Sustained production of NO and cGMP by endogenous iNOS has been shown to be anti-myofibroblastic, prevent accumulation of reactive oxygen species, cytokine release, and collagen deposition. However, well-designed trials with patients are needed [98]. Concerning the mechanism of action of tamoxifen, it was recently shown that in various models of fibrosis in other organs it suppresses production of ECM (mainly collagen) in mesangial cells, impairs human dermal fibroblast proliferation and function and attenuates wound contraction in wound healing [99]. Historically, a number of agents have been suggested for oral treatment of PD, such as potassium para-aminobenzoate, vitamin E, colchicine, pentoxifylline, and acetyl-L-carnitine which were critically discussed in other excellent reviews [100,101]. None of these compounds are recommended by the AUA [102]. The studies that investigated PDE5is all enlisted patients that already had stable plaques [103–105]. Despite not being endorsed by the AUA guidelines, it could be shown that tamoxifen exerted an effect in the early phase of PD [106,107] but not on established plaques [108]. This highlights the need to improve the design of clinical trials especially when treatment targets the early stage of PD. Additionally, studies need to be improved in terms of power, randomisation, and placebo controls. The lack of a non-invasive biomarker that could be measured in the serum or urine of the patient further complicates things which is an area that needs to be addressed not only in PD but fibrosis in general [109].Additionally, the dawn of affordable next-generation sequencing could have an impact on drug development as well. In 2017 Subramanian et al. described how high-throughput gene expression profiling technology can connect genes, drugs and disease states by virtue of common gene expression profiles (http://clue.io) [110]. This revolutionary software (L1000 platform: a next generation connectivity map) can integrate and process publicly available sequencing data in order to record the changes in cellular signatures and transcriptional regulation in response to chemical and genetic perturbation. This could be an innovative way to discover novel perturbagens and small molecules able to modulate a cluster of pathways with a high reproducibility and an accuracy similar to RNA sequencing. These compounds could then be used in screening assays, like the one developed by Ilg et al. [19].

Despite all the progress made in the past few years regarding PD, we need to strive to develop more physiologically relevant *in vitro* and *in vivo* models for its research. To mimic the complexity of the human situation more closely, we would need to resort to the development of novel co-culture systems, scaffolds and three-dimensional culture systems. Even though these can never perfectly represent the patient’s disease course, it would allow for a more relevant model to facilitate the translation of novel treatments from bench to bedside.

***Conclusion***

Historically, Peyronie’s disease has not been studied as widely as kidney, lung or hepatic fibrosis and our knowledge of its pathophysiology still remains relatively obscure. Nonetheless, recent breakthroughs using stem cells, next-generation sequencing and phenotypical screening assays bring us several steps closer to filling the gaps in our knowledge. In the near future, clinical trials will prove essential to translate this plethora of preclinical data into usable tools which can improve the lives of many of our patients.

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Figure Legend

Figure 1. This figure shows a proposed mechanism in the molecular regulation of Peyronie’s disease. Due to tissue damage and mechanical stress, various damage-associated molecular patterns (DAMPs) are released either from apoptotic/dying cells or the extracellular matrix. DAMP is an umbrella term for a variety of molecules such as high-mobility group box 1 (HMBGB1), S100 calcium-binding protein A/B (S100A/B), tenascin-C (TNC), heat-shock protein 70 (HSP70)... Binding of these ligands to e.g. toll-like receptors (mostly -2 and -4) can activate resident macrophages into their inflammatory phenotype. fibroblasts to produce chemotactic signals for the innate immunity (such as CCL-2 for macrophages). Macrophages of the M1 type are attracted to the site of injury and cause the initial inflammatory response produce chemotactic signals for the innate immunity (such as CCL-2 for macrophages).

Binding of DAMPs to TLR-2/-4 on the macrophage elicit several pro-inflammatory responses. TLR activates (i) NF-kB (as well as MAPK signaling, not depicted here) which causes the production of a wide array of pro-inflammatory cytokines (e.g. IL-1b, IL-2, IL-6 and TNF-α) and (ii) interferon-regulatory factors (IRF) 3 and 7 which produce chemotactic (e.g. type I interferons for the chemotaxis of T-helper 1 cells) and T-cell activating factors (CD80, 83 and 86).

In turn, T-helper 1 cells produce interferon-γ and IL-2 as their pro-inflammatory cytokines.

Moreover, macrophages can activate fibroblasts to produce chemotactic signals to maintain the positive feedback loop and (ii) initiate a myofibroblast phenotype transformation (through release of TGF-β1), causing wound contraction and extracellular matrix production, among other functions.