

# Alterations in the aqueous humor proteome in patients with a glaucoma shunt device

Arundhati Anshu,<sup>1,2</sup> Marianne O. Price,<sup>2</sup> Matthew R. Richardson,<sup>3</sup> Zaneer M. Segu,<sup>4</sup> Xianyin Lai,<sup>5</sup> Mervin C. Yoder,<sup>3</sup> Francis W. Price Jr<sup>1</sup>

<sup>1</sup>Price Vision Group, Indianapolis, IN; <sup>2</sup>Cornea Research Foundation of America, Indianapolis, IN; <sup>3</sup>Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN; <sup>4</sup>Department of Chemistry, Indiana University, Bloomington, IN; <sup>5</sup>Department of Cellular and Integrative Physiology, Indiana University School of Medicine, Indianapolis, IN

**Purpose:** To investigate whether implantation of a glaucoma shunt device leads to inappropriate accumulation of plasma derived proteins in the aqueous humor.

**Methods:** Aqueous humor samples were collected from 11 patients (study group) with a glaucoma shunt device undergoing either cataract surgery or a corneal transplant and 11 patients (control) with senile cataract undergoing routine cataract extraction. Of the study group, 9 had an Ahmed valve implant and 2 eyes had a Baerveldt implant. Tryptic digests of the mixture of proteins in aqueous humor (AH) were analyzed using Liquid Chromatography/Mass Spectrometry (LC-MS/MS). Proteins were identified with high confidence using stringent criteria and compared quantitatively using a label-free platform (IdentiQuantXL<sup>TM</sup>).

**Results:** We identified 135 proteins in the albumin-depleted fraction in both the study and control group AH. Using stringent criteria, 13 proteins were detected at a significantly higher level compared to controls. These proteins are known to play a role in oxidative stress, apoptosis, inflammation and/or immunity and include gelsolin (p=0.00005), plasminogen (p=0.00009), angiotensinogen (p=0.0001), apolipoprotein A-II (p=0.0002), beta-2-microglobulin (p=0.0002), dickkopf-3 (DKK-3; p=0.0002), pigment epithelium-derived factor (p=0.0002), RIG-like 7–1 (p=0.0002), afamin (p=0.0003), fibronectin 1 (FN1; p=0.0003), apolipoprotein A-I (p=0.0004), activated complement C4 protein (C4a; p=0.0004) and prothrombin (p=0.0004). Many of the identified proteins were novel proteins that have not been associated with glaucoma in prior studies. All but C4a (complement C4 is a plasma protein but not in an activated form) are known plasma proteins and the elevated levels of these proteins in the aqueous humor suggests a breach in the blood-aqueous barrier with passive influx into the anterior chamber of the eye.

**Conclusions:** The presence of these proteins in the aqueous humor suggests that glaucoma shunt device causes either a breach in blood-aqueous barrier or chronic trauma, increasing influx of oxidative, apoptotic and inflammatory proteins that could potentially cause corneal endothelial damage.

Glaucoma is an optic neuropathy characterized by progressive loss of retinal ganglion cells that lead to structural changes at the optic nerve head and functional visual loss. It is often, but not always, associated with increased intra-ocular pressure (IOP). According to the World Health Organization, it is the second leading cause of blindness in the world and accounts for 9%–12% of cases of blindness in the US. Management strategies include medical therapy usually in the form of topical anti-glaucoma medications to lower IOP. If IOP is resistant to medical therapy and/or there is progressive optic nerve damage, surgery is considered, usually in the form of trabeculectomy or a glaucoma shunt device.

Glaucoma has long been recognized as an important factor influencing corneal graft survival [1-5]. In our published series of over 4,000 full thickness penetrating keratoplasties, we identified pre-existing glaucoma as a risk factor for graft failure and other authors have reported similar outcomes [2,6,7]. High intra-ocular pressure (IOP) is not only detrimental to optic nerve function, it can also lead to corneal endothelial cell attrition. Glaucoma filtration surgery, although essential for preservation of visual function, has also been known to affect corneal graft survival adversely with several series citing poor longer-term graft survival especially in eyes with a glaucoma shunt device [8-10]. More recently, in eyes undergoing endothelial keratoplasty, glaucoma filtration surgery also had a significantly adverse effect on graft survival [11].

The mechanisms of corneal endothelial damage in eyes with a glaucoma shunt device are not fully understood. Glaucoma shunt devices can damage the corneal endothelium by mechanical means or by permitting retrograde entrance of inflammatory cells into the anterior chamber [12-15]. In addition, glaucoma shunt devices disrupt the blood–aqueous barrier and this could further increase influx of inflammatory mediators that could potentially cause corneal endothelial damage.

Correspondence to: Marianne Price, Ph.D., M.B.A., Executive Director, Cornea Research Foundation of America, 9002 North Meridian Street, Suite 212, Indianapolis, IN, 46260; Phone: (317) 814-2990; FAX: (317) 814-2806; email: marianneprice@cornea.org

Age	Sex	Type of surgery during aqueous humor tap
Study patients		
69	Female	Cataract
56	Male	Corneal transplant
31	Male	Cataract
56	Male	Corneal transplant
23	Male	Corneal transplant
74	Male	Corneal transplant
45	Male	Cataract
90	Female	Corneal transplant
49	Male	Corneal transplant
89	Male	Corneal transplant
71	Female	Repeat glaucoma shunt
ormal controls		
52	Male	Cataract
73	Male	Cataract
76	Female	Cataract
72	Male	Cataract
70	Male	Cataract
73	Male	Cataract
63	Female	Cataract
43	Female	Cataract
60	Female	Cataract
66	Female	Cataract
56	Female	Cataract

TABLE 1. CLINICAL DATA ON STUDY PATIENTS AND NORMAL CONTROLS.

Proteomics is one of the emerging techniques for biomarker discovery. Aqueous humor (AH) is the biologic fluid in the eye that has the task of protecting and supplying nutrition to the cornea, lens and trabecular meshwork (TM). A balance between production and drainage of AH is critical to maintaining normal IOP. The protein composition of AH has been shown to change dramatically in various ocular conditions such as corneal graft rejection [16], myopia [17], corneal dystrophies [18-20], and glaucoma [21-24]. Although the exact pathogenesis of glaucoma remains unclear, it is likely that alterations in the AH protein composition trigger signaling molecules that could modify the TM, increasing resistance to outflow and hence glaucoma [25,26].

With this background in mind, we decided to explore the AH proteomics in eyes with a pre-existing glaucoma shunt device to characterize the proteins that could potentially serve as biomarkers for not only glaucoma but also for corneal endothelial damage. The results of this study could potentially influence therapeutic strategies designed to improve longer-term graft survival in these high-risk eyes.

#### **METHODS**

Sample collection: Patients were selected and samples collected as previously described [27]. Briefly, study subjects

were either patients scheduled to undergo routine cataract surgery (controls) or patients with previous glaucoma shunt device scheduled to undergo corneal transplant or cataract surgery at a tertiary referral center, Price Vision Group (Indianapolis, IN). Exclusion criteria were as follows: history of conjunctivitis or any ocular infection within the previous 3 months and ongoing intraocular inflammation. An independent review board (IRB) approved the study and all subjects signed a written Informed Consent document. Before surgery, the patient's eye was anesthetized topically with proparacaine. A stab incision was made in the peripheral cornea, and 0.1 to 0.2 ml of anterior chamber fluid was aspirated using a 30-gauge needle. AH samples were stored frozen in liquid nitrogen until analysis. Any sample suspected of being contaminated with blood or iris pigment was discarded. Samples from 22 subjects were analyzed (11 cataract patients and 11 patients with glaucoma shunt device) as shown in Table 1.

*Materials:* Acetonitrile and ammonium bicarbonate were purchased from Fisher Scientific (Fair Lawn, NJ). Dithiothreitol (DTT) and iodoacetamide (IAA) were obtained from Bio-Rad Laboratories (Hercules, CA). Trypsin was purchased from Promega (Madison, WI). ProteoPrep immunoaffinity depletion kit was purchased from Sigma (St. Louis, MO). The following sample preparation and mass spectrometric analyses were performed at MetaCyt Biochemical Analysis Center (Bloomington, IN).

Depletion and protein assay: Depletion of albumin and IgG was performed using the ProteoPrep immunoaffinity depletion kit (Sigma) as described in instruction manual with some modification. As the depletion kit is designed for plasma samples and the protein content in AH is significantly lower, preliminary studies were performed to develop a protocol for optimal AH depletion, which resulted in enhanced protein identification (data not shown). Briefly, an estimation of material to be used to deplete albumin and IgG from AH was made using a BCA protein assay and quantification of albumin and IgG in AH samples relative to plasma assuming total protein content of 80 µg/µl and 75% albumin and IgG in plasma. The estimated amount of material by weight was measured from the ProteoPrep immunoaffinity column and transferred to an empty spin column, and depletion was performed as described in the instruction manual.

*Trypsin digestion:* Protein samples were subjected to tryptic digestion before analysis as follows: after thermal denaturation at 95 °C for 5 min, samples were reduced through the addition of DTT to a final concentration of 5 mM and incubated at 60 °C for 45 min. Alkylation was then followed by an addition of IAA to a final concentration of 20 mM for 45 min in the dark at room temperature. A second aliquot of DTT to about 10 mM. The samples were then incubated at room temperature for 30 min to quench the alkylation reaction. Next, trypsin was added (1:30 w/w) and microwave-assisted enzymatic digestion was performed at 45 °C for 15 min at the power of 50 W. Finally enzymatic digestion was quenched through the addition of 0.5  $\mu$ l of neat formic acid.

Instrumentation: Liquid chromatography tandem mass spectrometry (LC-MS/MS) analyses of the tryptic digests were performed using a Dionex 3000 Ultimate nano-LC system (Dionex, Sunnyvale, CA) interfaced to an LTQ Orbitrap hybrid mass spectrometer (Thermo Scientific, San Jose, CA). Prior to separation, a 4-ul aliquot of trypsin digestion (1 µg protein equivalent) was loaded onto a PepMap300 C18 cartridge (5 µm, 300 Å; Dionex) and eluted through the analytical column (150 mm×100 µm i.d, 200 Å pores) packed with C18 magic (Michrom Bioresources, Auburn, CA). Peptides originating from protein tryptic digests were separated using a reversed-phase gradient from 10%-55% B, 99.9% acetonitrile with 0.1% formic acid over 50 min for proteins isolated from the aqueous humor, at 500 nl/min flow rate and passed through an ADVANCE ionization source (Michrom Bioresources). The mass spectrometer was operated in an automated data-dependent mode that was switching between MS scan and CID-MS. In this mode, eluted LC products undergo an initial full-spectrum MS scan from m/z 300 to 2,000 in the Orbitrap at 15,000 mass resolutions, and subsequently CID-MS (at 35% normalized collision energy) was performed in the ion trap. The precursor ion was isolated using the data-dependent acquisition mode with a 2 m/z isolation width to select automatically and sequentially five most intense ions (starting with the most intense) from the survey scan. The total cycle (6 scans) was continuously repeated for the entire LC-MS run under data-dependent conditions with dynamic exclusion set to 60 s. Performing MS scanning in the Orbitrap offers high mass accuracy and accurate charge state assignment of the selected precursor ions.

## Protein identification and label-free quantification:

**Peptide and protein identification**—The acquired data were searched against the International Protein Index (IPI) human database (ipi.HUMAN.v3.69.fasta) using SEQUEST (v. Twenty-eight rev. 12) algorithms in Bioworks (v. 3.3). General parameters were set to: peptide tolerance 2.0 amu, fragment ion tolerance 1.0 amu, enzyme limits set as "fully enzymatic - cleaves at both ends," and missed cleavage sites set at 2. The searched peptides and proteins were validated by PeptideProphet [28] and ProteinProphet [29] in the Trans-Proteomic Pipeline (TPP, v. 3.3.0). Only proteins with probability  $\geq$ 0.9000 and peptides with probability  $\geq$ 0.8000 were reported.

**Protein quantification**—Protein quantification was performed using an in-house software package, IdentiQuantXL<sup>TM</sup>. The retention time of peptide for its intensity extraction was performed with an experiment-based algorithm RetentionTimeXL<sup>TM</sup>. The intensity of validated peptide was extracted and the protein quantification was calculated from peptide intensity.

*Statistical analysis:* The relative quantity of each protein was determined in each individual AH sample, and the results for the two groups were compared using the Student's *t*-test. A p-value <0.05 was considered to be statistically significant but then post-hoc adjustment of the p-value was performed using Holm-Sidak test to correct for multiple comparisons.

# RESULTS

We performed label-free quantitative mass spectrometry on AH samples derived from patients with and without prior glaucoma shunt surgery. AH samples were depleted of interfering abundant proteins such as albumin before LC-MSMS was used for protein identification and quantification. We identified 135 proteins in the albumin-depleted fraction (Table 2) with high confidence in the study as well as control group AH. After using stringent detection criteria, the AH in eyes with a prior glaucoma shunt device showed significantly increased levels of 13 proteins as shown in bold in Table 2. These proteins were pro-inflammatory (plasminogen [p=0.00009], angiotensinogen [p=0.0001], prothrombin [p=0.0004] and C4a protein [p=0.0004]); anti-oxidative/anti-apoptotic (gelsolin [p=0.00005], afamin [p=0.0002], and dickkopf-3

[DKK-3; p=0.0002]); anti-inflammatory (apolipoprotein A-I [apo A-1; p=0.0004], and apolipoprotein A-II [apo A-II; p=0.0002]); or other roles (fibronectin 1 [FN1; p=0.0003], RIG-like 7–1 [p=0.0002], and beta-2-microglobulin [p=0.0002]). The percent of protein sequence covered by the peptides identified with high confidence is listed for each protein along with the number of unique sequences as well as the fold-change compared to the protein level in control patients.

### DISCUSSION

This study highlights for the first time the differential expression of AH proteins in eyes with a glaucoma shunt device compared to normal controls. Many of the identified proteins except fibronectin [30] and PEDF [31] are novel proteins that to our knowledge have not been detected in the AH of glaucoma patients. Interestingly, all of the identified proteins except C4a are known plasma proteins and increased expression in the AH suggests a breach in the blood aqueous barrier caused by a glaucoma drainage device. AH proteome changes identified in this study may not only help elucidate glaucoma pathogenesis but also shed light on the possible mechanisms that result in corneal endothelial damage and hence accelerated corneal transplant failure in eyes with glaucoma surgery.

We found a significant upregulation of complement C4a (fold change, 5; p=0.0004), an activated fragment of complement component C4. Complement activation is under the tight control of complement inhibitors; uncontrolled complement activation can cause cell lysis and inflammation while a balanced activation is necessary for clearing tissue debris and in healing. Imbalance in complement regulation has also been suggested to contribute to the neurodegenerative damage characteristic of glaucoma [32]. Activated complement in the AH, as seen in this study, could possibly cause corneal endothelial damage via direct cell lysis and inflammation.

There was evidence of enhanced fibrinolytic and coagulative activity in the AH as suggested by differential expression of prothrombin (fold change, 2.9; p=0.0004), angiotensinogen (fold change, 4.4; p=0.0001) and plasminogen (fold change, 6.2; p=0.00005). O'Brien et al. [33] have reported elevated prothrombin levels in the plasma of patients with primary open angle glaucoma and have implicated this hypercoagulable state in glaucoma pathophysiology. Angiotensinogen is a component of the renin-angiotensin (RAS) system and plays a role in the regulation of AH dynamics [34]. Plasminogen is a component of the plasmin system, and the main physiologic inhibitor of the plasmin system is plasminogen activator inhibitor-1 (PAI-1). Elevated levels of PAI-1 have been reported in the AH of glaucoma patients thus contributing to glaucoma pathogenesis by reducing proteolysis of the extracellular

matrix in the TM and increasing resistance to outflow [35]. Prothrombin is also recognized as a biomarker of systemic sepsis and inflammation [36] and elevated levels in the AH suggest increased inflammation due to a breach in the blood-aqueous barrier caused by the glaucoma shunt device. Increased inflammation has been shown to stimulate increased synthesis of pro-inflammatory cytokines like interleukin-1 and tumor necrosis factor by the corneal endothelium [37,38] leading to corneal endothelial damage.

Afamin (fold change, 3.3; p=0.0003) and gelsolin (fold change, 4.7; p=0.00005) were the 2 extracellular chaperones found to be differentially expressed in the AH of patients with glaucoma shunt device compared to normals. Afamin is a member of the albumin multigene family with vitamin Ebinding properties. It plays a crucial role in protecting against oxidative damage and displays neuroprotective activity not only by virtue of binding and transporting vitamin E but also on its own [39]. Gelsolin is an anti-oxidant and anti-apoptotic protein that has been implicated as a therapeutic target in Alzheimer disease since it has been shown to reduce amyloid load by inhibiting Abeta fibrillization in animal studies [40]. A decreased level of gelsolin has been observed in patients with sepsis, myocardial infarction and inflammation while an increased level has been noted in amyloidosis [41,42], so it could be a secondary response to increased amyloid load The upregulation of these extracellular chaperones is likely a response to the increased oxidative stress in the aqueous secondary to glaucoma. Oxidative stress has been recognized as the main pathogenic factor underlying open angle glaucoma [43-45]. It is likely that this may also contribute to corneal endothelial damage. Increased expression of these proteins may reflect the inability of these extracellular chaperones to completely inhibit oxidative and apoptotic damage both in the TM as well as the corneal endothelium.

Pigment epithelium-derived factor (PEDF), a member of the serpin family of proteins and expressed in all ocular tissues of the human eye, was significantly upregulated in eyes with a glaucoma shunt device (fold change, 4.6; p=0.0002). It is neuroprotective and anti-angiogenic and recently recognized as an endogenous anti-inflammatory factor [46,47]. Significantly reduced levels have been reported in advanced glaucoma AH compared to normal controls [31]. Additionally in animal models, PEDF has been shown to protect retinal ganglion cells from pressure-induced ischemia [48]. Our finding of significantly increased expression of PEDF is intriguing and leads us to speculate that perhaps this protein serves a protective role in the AH.

The function of Dickkopf-3 (Dkk3) is unclear; however, Jung et al. [49] suggest that it may acts as an anti-apoptotic molecule by decreasing intracellular levels of reactive oxygen species. Recently Nakamura et al. [50] have demonstrated that it may play a cytoprotective role in the retina by reducing caspase activity and hence protecting against apoptosis. Its

Gelsolin Plasminogen Angiotensinogen Apolipoprotein A-II Beta-2-microglobulin cDNA FLJ33633 fis, clone BRAMY2022786, highly similar to Homo sapiens dickkopf-3 (DKK-3) mRNA cDNA FLJ35545, highly similar to Dickkopf-related protein 3 Pigment epithelium-derived factor RIG-like 7–1 Afamin CDNA FLJ53292, highly similar to Homo sapiens fibronectin 1 (FNI), transcript variant 5, mRNA	coverage (%) 5.12 5.12 21.98 16.49 64 18.49 30.7 38.28 38.28 38.28 33.39 13.86 23.39 13.86 2.17 2.17	unique sequences 5 6 6 1 1 2 1 2 2 1 1 1 7	normal 97.38 66.75 50.43 33.81 43.93	shunt 42.91	change in shunt patients 47	(shunt versus normal) 0.000050	protein
Gelsolin Plasminogen Angiotensinogen Apolipoprotein A-H Beta-2-microglobulin Boha FLJ33633 ffs, clone BRAMY2022786, highly similar to Homo appiens dickkopf-3 (DKK-3) mRNA appiens dickkopf-1 (DKK-3) mRNA appiens dickkopf-1 (DKK-3) mRNA appient epithelium-derived factor Figment epithelium-derived factor Afamin Afamin Afamin Afamin Apoliporotein A-I	(%) 5.12 5.12 21.98 16.49 64 18.49 30.7 38.28 38.28 38.28 33.39 13.86 23.39 23.39 23.39 23.39	sequences 2 10 12 12 2 17 17	97.38 66.75 50.43 71.48 33.81 43.93	42.91	shunt patients 4 7	versus normal) 0.000050	;
Gelsolin Plasminogen Angiotensinogen Apolipoprotein A-H Beta-2-microglobulin Boha FLJ33633 fis, clone BRAMY2022786, highly similar to Homo apiens dickkopf-3 (DKK-3) mRNA 2DNA FLJ52545, highly similar to Dickkopf-related protein 3 Figment epithelium-derived factor Figment epithelium-derived factor Afamin Afamin Afamin Afamin Afanivation fighly similar to Homo sapiens fibronectin 1 (FN1), transcript variant 5, mRNA	5.12 21.98 16.49 64 18.49 30.7 38.28 38.28 33.39 13.86 23.39 23.39 23.39 23.39 23.39	1 - 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	97.38 66.75 50.43 71.48 33.81 43.93	42.91	patients 4 7	normal) 0.000050	;
Gelsolin Plasminogen Angiotensinogen Apolipoprotein A-H Beta-2-microglobulin Bota-2-microglobulin DNA FLJ3533 ffs, clone BRAMY2022786, highly similar to Homo apiens dickkopf-3 (DKK-3) mRNA 2DNA FLJ55245, highly similar to Dickkopf-related protein 3 Pigment epithelium-derived factor Pigment epithelium-derived factor RIG-like 7–1 Afamin Afamin FND, transcript variant 5, mRNA Apoliporotein A-1	5.12 21.98 16.49 64 18.49 30.7 38.28 38.28 13.86 13.86 23.39 13.86 2.17 2.17	2 <u>0</u> 2 2 4 4 <u>7</u> 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	97.38 66.75 50.43 71.48 33.81 43.93	42.91	47	0.000050	
Plasminogen Angiotensinogen Apolipoprotein A-H Beta-2-microglobulin EDNA FLJ35633 frs, clone BRAMY2022786, highly similar to Homo apiens dickkopf-3 (DKK-3) mRNA apiens dickkopf-3 (DKK-3) mRNA EDNA FLJ55545, highly similar to Dickkopf-related protein 3 Pigment epithelium-derived factor RIG-like 7–1 Afamin Afamin EDNA FLJ53292, highly similar to Homo sapiens fibronectin 1 FN1), transcript variant 5, mRNA Apoliporotein A-1	21.98 16.49 64 18.49 30.7 38.28 38.28 13.86 13.86 2.17 2.17 2.17	0 0 0 0 0 0 0 0 0 0 0 0 0 0	66.75 50.43 71.48 33.81 43.93		F		Yes
Angiotensinogen Apolipoprotein A-H Beta-2-microglobulin EDNA FLJ33633 frs, clone BRAMY2022786, highly similar to Homo apiens dickkopf-3 (DKK-3) mRNA 2DNA FLJ52545, highly similar to Dickkopf-related protein 3 Pigment epithelium-derived factor RIG-like 7–1 Afamin Afamin FND, transcript variant 5, mRNA Apolloprotein A-I	16.49 64 18.49 30.7 38.28 38.28 23.39 13.86 13.86 2.17 2.17	volta 420vi 1	50.43 71.48 33.81 43.93	47.85	6.2	0.000000	Yes
Apolipoprotein A-II Beta-2-microglobulin Bota-2-microglobulin DNA FLJ33633 fis, clone BRAMY2022786, highly similar to Homo apiens dickkopf-3 (DKK-3) mRNA DNA FLJ52545, highly similar to Dickkopf-related protein 3 Pigment epithelium-derived factor RIG-like 7–1 Afamin Afamin DNA FLJ53292, highly similar to Homo sapiens fibronectin 1 FN1), transcript variant 5, mRNA Apoliporotein A-1	64 18.49 30.7 38.28 38.28 23.39 13.86 2.17 2.17 2.17	9 T 4 4 7 7 8 7 7 1 9 1 9 1 9 1 9 1 9 1 9 1 9 1 9 1 9	71.48 33.81 43.93	46.49	4.4	0.000100	Yes
Beta-2-microglobulin :DNA FLJ33633 fis, clone BRAMY2022786, highly similar to Homo apiens dickkopf-3 (DKK-3) mRNA :DNA FLJ52545, highly similar to Dickkopf-related protein 3 Pigment epithelium-derived factor RIG-like 7-1 Afamin :DNA FLJ53292, highly similar to Homo sapiens fibronectin 1 (FN1), transcript variant 5, mRNA Apolitorrotein A-1	18.49 30.7 18.13 38.28 23.39 13.86 2.17 2.17 2.17	14 42001 1	33.81 43.93	58.76	18.5	0.000200	Yes
<ul> <li>DNA FLJ33633 fis, clone BRAMY2022786, highly similar to Homo apiens dickkopf-3 (DKK-3) mRNA</li> <li>DNA FLJ52545, highly similar to Dickkopf-related protein 3</li> <li>Pigment epithelium-derived factor</li> <li>RIG-like 7–1</li> <li>Afamin</li> <li>DNA FLJ53292, highly similar to Homo sapiens fibronectin 1</li> <li>(FN1), transcript variant 5, mRNA</li> <li>Apolinoprotein A-1</li> </ul>	30.7 18.13 38.28 23.39 13.86 2.17 2.17	4 42001 1	43.93	49.13	5.7	0.000200	Yes
sapiens dickkopf-3 (DKK-3) mRNA :DNA FLJ52545, highly similar to Dickkopf-related protein 3 Pigment epithelium-derived factor RIG-like 7–1 Afamin :DNA FLJ53292, highly similar to Homo sapiens fibronectin 1 (FN1), transcript variant 5, mRNA Apolinoprotein A-1	18.13 38.28 23.39 13.86 2.17 2.17	4 <b>1</b> 2 2 5 1 7 1 7 1 7 1 7 1 7 1 7 1 7 1 7 1 7 1		45.25	4	0.000200	Yes
CDNA FLJ52545, highly similar to Dickkopf-related protein 3 Pigment epithelium-derived factor RIG-like 7–1 Afamin CDNA FLJ53292, highly similar to Homo sapiens fibronectin 1 CN1), transcript variant 5, mRNA Apolinoprotein A-1	18.13 38.28 23.39 2.17 2.17 54.31	4 2 2 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2					
Pigment epithelium-derived factor RIG-like 7–1 Afamin DNA FLJ53292, highly similar to Homo sapiens fibronectin 1 (FN1), transcript variant 5, mRNA Apolinoprotein A-1	38.28 23.39 13.86 2.17 54.31	12 - 2 - 12	43.93	45.25	4	0.000200	Yes
RIG-like 7–1 Afamin 2DNA FLJ53292, highly similar to Homo sapiens fibronectin 1 (FN1), transcript variant 5, mRNA Apolinoprotein A-1	23.39 13.86 2.17 54.31	1 1 2 2	54.02	48.22	4.6	0.000200	Yes
Afamin EDNA FLJ53292, highly similar to Homo sapiens fibronectin 1 (FN1), transcript variant 5, mRNA Apolinoprotein A-I	13.86 2.17 54.31	5 11 17	35.69	52.57	7.2	0.000200	Yes
cDNA FLJ53292, highly similar to Homo sapiens fibronectin 1 (FN1), transcript variant 5, mRNA Apolinoprotein A-I	2.17 54.31	1 17	53.94	45.3	3.3	0.000300	Yes
(FN1), transcript variant 5, mRNA Apolipoprotein A-I	54.31	17	53.67	53.43	6.2	0.000300	Yes
Apolipoprotein A-I	54.31	17					
			49.82	55.18	6.4	0.000400	Yes
C4A protein	18.43	18	60.51	50.69	4.1	0.000400	N0
Prothrombin (Fragment)	18.81	7	59.4	43.88	2.9	0.000400	Yes
similar to C4A protein isoform 2	15.9	15	59.85	45.91	3.3	0.000400	No
Ceruloplasmin	32.68	24	51.22	52.5	4.5	0.000500	
Hemopexin	53.9	17	73.75	56.72	6.2	0.000500	
Kininogen-1, Isoform LMW	26.93	8	49.09	47.4	3.2	0.000600	
KNG1 protein	34.36	7	48.72	47.54	3.1	0.000700	
V-acetylmuramoyl-L-alanine amidase	4.69	7	64.87	53.66	4.2	0.000700	
Protein	49.53	"	52.92	61.2	7.2	0.000800	
Complement factor B	6.45	0	24.5	55.96	4.4	0.00000.0	
Retinol-binding protein 4	33.33	4	63.72	53.93	3.9	006000.0	
Serotransferrin	67.62	50	66.88	50.61	3.4	006000.0	
Antithrombin-III	43.1	14	62.13	59.34	4.7	0.001000	
DNA FLJ59472, highly similar to Tripeptidyl-peptidase 1	7.8	1	28.97	41.42	2.3	0.001000	
Complement C3 (Fragment)	29.95	34	57.03	54.67	3.6	0.001000	
Complement component 4A	20.3	20	59.62	59.21	5	0.001000	
Corticosteroid-binding globulin	10.12	7	45.96	61.64	5.4	0.001000	
Putative uncharacterized protein	17.99	2	34.29	56.42	4.3	0.001000	
Putative uncharacterized protein AZGP1	26.87	4	66.28	55.65	4	0.001000	
Putative uncharacterized protein C4A	21.33	21	58.55	59.2	5.2	0.001000	
similar to complement component 3	4.87	1	42.7	58.4	4.7	0.001000	
similar to complement component 4B (Childo blood group), partial	2.85	1	92.62	61.48	9	0.001000	
Vitronectin	13.6	4	56.8	59.77	5.1	0.001000	
Alpha-1-acid glycoprotein 2	39.8	8	74.23	60.87	4.2	0.002000	
Alpha-1B-glycoprotein	35.96	11	64.92	68.72	6.5	0.002000	
alpha-2-glycoprotein 1, zinc precursor	40.6	6	55.39	51.01	2.9	0.002000	
Alpha-2-macroglobulin	11.47	11	56.79	54.7	3.3	0.002000	
Beta-crystallin B2	19.51	4	95.69	65.53	5.7	0.002000	
DNA FLJ55673, highly similar to Complement factor B	5.45	4	44.43	58.6	4.2	0.002000	
Complement C4-A	20.07	20	58	62.3	5	0.002000	
Complement C4-B	18.18	18	59.41	55.54	3.5	0.002000	
inter-alpha-trypsin inhibitor heavy chain H4	7.33	4	66.74	67.97	7.6	0.002000	
Kininogen-1, Isoform HMW	15.84	7	50.67	51.24	2.9	0.002000	
	(Fragment) A protein isoform 2 Isoform LMW I moyl-L-alanine amidase moyl-L-alanine amidase factor B ig protein 4 in 111 111 112 112 112 112 111 111 112 112		<b>13.86</b> <b>54.31</b> <b>18.81</b> <b>18.81</b> <b>18.81</b> <b>18.81</b> <b>18.81</b> <b>18.81</b> <b>18.81</b> <b>18.81</b> <b>18.9</b> <b>26.93</b> <b>33.33</b> <b>4.69</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>7.33</b> <b>39.8</b> <b>10.12</b> <b>20.3</b> <b>29.5</b> <b>10.12</b> <b>20.3</b> <b>20.3</b> <b>20.3</b> <b>20.3</b> <b>20.3</b> <b>20.3</b> <b>20.3</b> <b>20.3</b> <b>20.3</b> <b>20.3</b> <b>20.3</b> <b>20.3</b> <b>20.6</b> <b>21.33</b> <b>39.8</b> <b>21.33</b> <b>20.7</b> <b>21.33</b> <b>20.07</b> <b>21.33</b> <b>21.33</b> <b>21.34</b> <b>21.33</b> <b>39.8</b> <b>21.33</b> <b>21.35</b> <b>21.33</b> <b>39.8</b> <b>21.33</b> <b>21.33</b> <b>21.35</b> <b>21.33</b> <b>39.8</b> <b>21.33</b> <b>21.35</b> <b>21.35</b> <b>21.35</b> <b>21.35</b> <b>21.35</b> <b>31.35</b> <b>32.96</b> <b>33.59</b> <b>40.6</b> <b>51.6</b> <b>51.33</b> <b>35.96</b> <b>51.33</b> <b>35.96</b> <b>51.33</b> <b>35.96</b> <b>51.33</b> <b>35.96</b> <b>51.33</b> <b>35.96</b> <b>51.33</b> <b>35.96</b> <b>51.33</b> <b>35.96</b> <b>51.33</b> <b>35.96</b> <b>51.33</b> <b>35.96</b> <b>51.33</b> <b>35.96</b> <b>51.33</b> <b>35.96</b> <b>51.33</b> <b>35.96</b> <b>51.33</b> <b>35.96</b> <b>51.33</b> <b>51.33</b> <b>51.34</b> <b>51.33</b> <b>51.34</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b>51.35</b> <b></b>	13.86       5         2.17       1         5.4.31       17         15.9       15.9         15.9       15.9         15.9       15.9         15.9       15.9         15.9       15.9         15.9       15.9         15.9       15.9         15.9       15.9         26.93       34.36         26.93       34.36         26.93       34.36         26.93       34.36         26.45       2.1         26.93       34.36         49.53       3.4         20.33       3.3         20.33       3.3         20.33       3.3         21.012       2.2         27.3       4.4         26.87       1         27.3       2.1         28.5       21         21.33       2.1         25.45       2.1         26.67       2         27.3       2.1         28.4       2.1         29.5       2.1         20.07       2.4         21.4       2.1         23.5	13.36 $5.17$ $1$ $5.3.94$ $2.17$ $1$ $17$ $9.82$ $8.43$ $17$ $17$ $5.9.4$ $15.9$ $15$ $5.9.4$ $15.9$ $17$ $7$ $5.9.4$ $15.9$ $17$ $7$ $5.9.4$ $15.9$ $17$ $7$ $5.9.4$ $15.9$ $17$ $7$ $5.9.85$ $53.9$ $17$ $7$ $5.9.85$ $53.9$ $17$ $7$ $5.9.85$ $53.9$ $17$ $7$ $5.9.85$ $53.0$ $22$ $24.5$ $50.621$ $26.93$ $3$ $2$ $24.5$ $57.03$ $22$ $24.5$ $50.621$ $20.33$ $20$ $2$ $64.87$ $7.8$ $1$ $144$ $62.13$ $7.8$ $1$ $144$ $62.13$ $7.8$ $20.3$ $22$ $24.5$ $20.3$ $20.3$ $22$ $24.5$ $20.3$ $20.3$ $22$ $24.5$ $20.3$ $20.3$ $22$ $24.5$ $20.3$ $20.3$ $22$ $24.5$ $20.3$ $20.3$ $22$ $24.5$ $20.3$ $21.33$ $21$ $28.97$ $20.3$ $22$ $24.5$ $56.62$ $21.33$ $21$ $28.5$ $21.33$ $21$ $28.5$ $21.33$ $21$ $28.5$ $21.33$ $21$ $28.5$ $21.35$ $28.5$ $24.5$ $22.53$ $22.56$ $22.52.52$ $23.545$ $22.56$ $22.52.52$ <tr< td=""><td>13.8655.04<math>45.3</math><math>2.17</math>1<math>5.04</math><math>45.3</math><math>54.31</math>17<math>9.82</math><math>55.18</math><math>18.43</math>18<math>0.51</math><math>50.69</math><math>18.43</math>15<math>59.4</math><math>45.3</math><math>15.9</math>15<math>59.4</math><math>43.88</math><math>15.9</math>17<math>59.4</math><math>43.88</math><math>15.9</math>17<math>59.4</math><math>43.88</math><math>15.9</math>26.938<math>49.09</math><math>47.4</math><math>32.68</math>24<math>51.22</math><math>50.69</math><math>33.33</math>2<math>24.87</math><math>51.22</math><math>53.33</math>3<math>22.95</math><math>56.72</math><math>53.33</math>4<math>60.51</math><math>59.34</math><math>49.69</math>2<math>64.87</math><math>51.22</math><math>56.72</math><math>49.25</math><math>56.72</math><math>49.53</math>3<math>32.292</math><math>61.64</math><math>17</math><math>12</math><math>64.87</math><math>57.03</math><math>56.70</math><math>56.88</math><math>50.61</math><math>64.75</math><math>59.34</math><math>41.42</math><math>7.8</math><math>1</math><math>28.97</math><math>7.8</math><math>1</math><math>28.97</math><math>7.8</math><math>1</math><math>28.97</math><math>17.99</math><math>56.42</math><math>20.33</math><math>21</math><math>28.97</math><math>21.33</math><math>21</math><math>28.95</math><math>56.87</math><math>44.23</math><math>56.42</math><math>21.33</math><math>21</math><math>28.55</math><math>59.54</math><math>59.24</math><math>11.47</math><math>111</math><math>22.13</math><math>56.87</math><math>59.24</math><math>21.33</math><math>21</math><math>58.55</math><math>59.56</math><math>56.79</math><math>56.87</math><math>56.79</math><math>56.87</math><math>56.79</math><math>56.87</math><math>56.79</math><math>56.87</math></td><td>1.3.66         5         5.3.94         4.5.3         5.3.67         5.3.43         6.2           <math>2.17</math>         1         <math>5.3.67</math> <math>5.3.43</math> <math>6.2</math> <math>5.3.43</math> <math>6.2</math> <math>3.43</math>         17         <math>9.82</math> <math>55.18</math> <math>6.4</math> <math>4.13</math> <math>8.33</math> <math>5.0.69</math> <math>4.11</math> <math>18.81</math>         17         <math>9.82</math> <math>55.18</math> <math>6.4</math> <math>5.3.43</math> <math>6.2</math> <math>5.3.43</math> <math>5.2.9</math> <math>6.2</math> <math>5.3.33</math> <math>6.4</math> <math>4.3.33</math>&lt;</td></tr<>	13.8655.04 $45.3$ $2.17$ 1 $5.04$ $45.3$ $54.31$ 17 $9.82$ $55.18$ $18.43$ 18 $0.51$ $50.69$ $18.43$ 15 $59.4$ $45.3$ $15.9$ 15 $59.4$ $43.88$ $15.9$ 17 $59.4$ $43.88$ $15.9$ 17 $59.4$ $43.88$ $15.9$ 26.938 $49.09$ $47.4$ $32.68$ 24 $51.22$ $50.69$ $33.33$ 2 $24.87$ $51.22$ $53.33$ 3 $22.95$ $56.72$ $53.33$ 4 $60.51$ $59.34$ $49.69$ 2 $64.87$ $51.22$ $56.72$ $49.25$ $56.72$ $49.53$ 3 $32.292$ $61.64$ $17$ $12$ $64.87$ $57.03$ $56.70$ $56.88$ $50.61$ $64.75$ $59.34$ $41.42$ $7.8$ $1$ $28.97$ $7.8$ $1$ $28.97$ $7.8$ $1$ $28.97$ $17.99$ $56.42$ $20.33$ $21$ $28.97$ $21.33$ $21$ $28.95$ $56.87$ $44.23$ $56.42$ $21.33$ $21$ $28.55$ $59.54$ $59.24$ $11.47$ $111$ $22.13$ $56.87$ $59.24$ $21.33$ $21$ $58.55$ $59.56$ $56.79$ $56.87$ $56.79$ $56.87$ $56.79$ $56.87$ $56.79$ $56.87$	1.3.66         5         5.3.94         4.5.3         5.3.67         5.3.43         6.2 $2.17$ 1 $5.3.67$ $5.3.43$ $6.2$ $5.3.43$ $6.2$ $3.43$ 17 $9.82$ $55.18$ $6.4$ $4.13$ $8.33$ $5.0.69$ $4.11$ $18.81$ 17 $9.82$ $55.18$ $6.4$ $5.3.43$ $6.2$ $5.3.43$ $5.2.9$ $6.2$ $5.3.33$ $6.4$ $4.3.33$ <

© 2011 Molecular Vision

$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	Ductoin ID	Ductoin name	I ABLE 2. CONTINUED. Drofoin	Number of	(70) (1)	(70) A.J	EALA	onlos a	Dlasma
ConstructionConstructionConstructionConstructionParties underactical protein DKC2/06600220929962.2127.7536Rises protectaticCDNA FL3075, Bighy similar to Certalphastin27.21927.753636CDNA FL3075, Bighy similar to Certalphastin27.2120.0127.75363646CDNA FL3075, Bighy similar to Certalphastin27.753075.76364646CDNA FL3075, Bighy similar to Certalphastin27.0120.0127.75364646CDNA FL3075, Bighy similar to Complement compact27.1127.6127.75364647Station similar to Complement compact27.1127.6127.75364137Station similar to Complement compact27.3127.6127.67364137Station similar to Complement compact27.3127.6127.67364137Station similar to Complement compact27.3127.6127.67364137Station similar to Complement compact27.3127.6127.67363641Station similar to Complement compact27.3127.6127.572627.5536Station similar to Complement compact27.5127.552627.553637.5536Station similar to Complement compact27.5127.552627.553637.5536Station similar to Complement compact27.51			coverage	unique	normal	shunt	change in	eshunt (shunt	protein
Putative undvanced root protection of protection of matrix undvanced root protection of matrix undvanced protection RKZ p6660(135)         9.88			(%)	sedneuces			shunt natiante	Versus normal)	
Alter partentic         134         1         227         616         48           Alter partentic         Alter partentic         236         7         735         7         716         711           Complement convent CBI Critich blood group)         236         7         735         9         756         27         716         711           Complement convent CBI Critich blood group)         236         7         735         9         756         6412         716	IP100384938	Putative uncharacterized protein DKFZn686N02209	29.88	6	68.21	57.76	3.6	0.002000	
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	IP100014048		13.46	. —	52.72	61.62	4.8	0.002000	
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	IP100553177	Alpha-1-antitrypsin	66.27	30	75.69	68.19	5.9	0.003000	
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	IP100947307	cDNA FLJ58075, highly similar to Ceruloplasmin	15.75	6	75.54	71.62	7.1	0.003000	
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	IPI00892604	Complement component C4B (Childo blood group) 2	26.09	27	57.45	64.62	4.5	0.003000	
Patrix         Details $(6, 5)$ <	IPI00013179	Prostaglandin-H2 D-isomerase	32.63	ς	59.4	52.56	2.7	0.003000	
13 4.Du protein       6.46       5       72.67       68.22       4.4         13 4.Du protein       5.08       31       22.37       56.3       4         Setup specien       26.08       31       22.39       56.4       4         Setup specien       26.08       31       22.33       37.39       56.4       4         26.bla protein       26.bla protein       27.33       1       22.43       56.6       4       4         26.bla protein       31.8.bla protein       27.33       1       22.43       56.6       4       4         26.bla protein       31.8.bla protein       27.35       65.4       4       4       57.33       56.6       4       4       57.35       56.6       4       4       57.35       56.6       4       4       57.35       56.6       4       4       57.35       56.6       4       4       57.35       56.6       57.35       56.6       57.35       56.6       57.35       56.6       57.35       56.6       57.35       56.6       57.35       56.6       57.35       56.7       57.35       56.7       57.35       56.7       57.35       56.7       57.35       56.7       57.7 <td< td=""><td>IPI00930124</td><td>Putative uncharacterized protein DKFZp686C11235</td><td>24.1</td><td>L</td><td>68.59</td><td>60.18</td><td>3.6</td><td>0.003000</td><td></td></td<>	IPI00930124	Putative uncharacterized protein DKFZp686C11235	24.1	L	68.59	60.18	3.6	0.003000	
Bit Differential         Differential	IPI00947496	124 kDa protein	6.46	S - S	72.67	68.22	4	0.004000	
Happejoin-related protein         208         7         4871         6778         46           Starm album         265 Mark Huston         233         3         7479         758         64           Starm album         265 Mark Huston         253         3         7479         758         64           Starm album         353         1         253         3         7479         758         66           3 Aby Fuzzim         13 Aby protein         273         14         253         559         6564         41           3 Starm album         13 Aby protein         273         14         253         559         6564         41           Starm album         33         3         3         3         3         3         3         3         3           Yianu Debioding protein         3         4262         17         623         66         3         3           ANTCHYMORY         ANTCHYMORY         200         33         3	IP100939333	86 kDa protein	11.13	S.	57.33	57.59	ς	0.004000	
Series         31 $0.23$ 31 $0.23$ 31 $0.23$ 31 $0.23$ 31 $0.23$ 31 $0.23$ 31 $0.24$ $5.68$ $0.41$ 13         Apblippoptent ALV         3737         14 $0.245$ $5.68$ $6.14$ $3$ 13         Apblippoptent ALV         3737         14 $0.245$ $5.68$ $2.14$ $3.56$ $6.114$ $3$ 13         Numegen-1 Isotom 3 $2.26$ 7 $5.66$ $7$ $5.66$ $4.113$ $3.75$ $6.114$ $3$ Viramin Dipropretin ALP         Numerator $3.75$ $2.66$ $7$ $5.66$ $3.66$	IP100477597	Haptoglobin-related protein	20.98	7	48.71	67.78	4.6	0.004000	
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	IPI00745872	Serum albumin	56.98	31	62.39	65.64	4	0.004000	
cDAA FL3739, highly similar to Complement C3         5.38         5         7,79         758         6.2           Apolipopretin AVV kinnin D-binding protein         3,737         14         6,545         5,598         2,64           Apolipopretin AVV kinnin D-binding protein         3,556         7         3,556         6,14         3           Protein AMBP         266         7         3,556         6,14         3           Protein AMBP         250         7         3,556         6,14         3           ONA FL3553, offs, clone TEST12003131, highly similar to ALPHA-1.         4333         16         51,65         8656         36           ONA FL3553, offs, clone TEST12003131, highly similar to ALPHA-1.         4333         16         51,65         8656         36           ANTICHYMOTRYPSIN         Complement for extram blumin         222         17         15,65         86         33           OND AFL3573, fist, clone TONG200958, highly similar to ALPHA-1.         4333         33,17         15         34,9         7           Distribution transferized protein 1         233         24         23         24         23           Complement component 6         24         33,17         15         33,17         35         34,38	IPI00796888	26 kDa protein	7.76	1	28.92	68.46	4.1	0.005000	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	IPI00942927	cDNA FLJ57339, highly similar to Complement C3	5.28	С	74.79	75.8	6.2	0.005000	
Apolipoprotein A-IV         37.3         14         62.49         60.08         4.1           Training Debinding         Viaming Debinding         26.6         7         35.6         61.14         3           Protein AMP         Total Debinding         26.6         7         53.65         64.73         2.4           Protein AMP         CDMA FLJ3730 fix, clow TESTI2003131, highly similar to ALPHA-1.         45.35         16         51.65         68.56         3.6           AVTICHTWOTRYPSN         20NA FLJ3791 fix, clow TESTI2003131, highly similar to ALPHA-1.         45.35         16.6         51.65         88.61         13         2.4           COMA FLJ3791 fix, clow TESTI2003131, highly similar to ALPHA-1.         2.23         1         101.32         88.9         64.87         3.3           Complement component of precision         2.01         7         2.08         8.3         3.3           Parame voltaracterized protein f2         2.01         7         2.01         3.3         3.17         3.3 <td>IPI00796830</td> <td>13 kDa protein</td> <td>10.53</td> <td>1</td> <td>63.45</td> <td>55.98</td> <td>2.6</td> <td>0.006000</td> <td></td>	IPI00796830	13 kDa protein	10.53	1	63.45	55.98	2.6	0.006000	
Relingent         Solution         Solutis         Solution         Solution	IPI00304273	Apolipoprotein A-IV	37.37	14	62.49	69.08	4.1	0.006000	
Vitamin D-binding protein         Q.62         17         G.2.8         76.48         5.7           Protein AMR         Constraints protein $7201$ $4.53$ $5.6$ $5.53$ $5.6$ ANTICHYNOTRYPSIN         CONA FLJ5730 fig. cheer TEST12003131, highly similar to ALPHA-1. $43.53$ $6.6$ $5.53$ $5.6$ $5.75$ $2.64$ $5.75$ $2.64$ $5.75$ $2.64$ $5.75$ $2.64$ $5.75$ $2.64$ $5.75$ $2.64$ $5.75$ $2.64$ $5.75$ $2.64$ $5.75$ $2.64$ $5.75$ $2.64$ $5.75$ $2.64$ $5.75$ $2.64$ $5.75$ $2.64$ $6.75$ $2.64$ $6.75$ $2.64$ $2.52$ $2.24$ <	IPI00924859	kininogen-1, Isoform 3	26.6	7	53.65	61.14	С	0.006000	
Protein AMBP         Trol         17.61         4         78.76         46.73         2.4           Protein AMBP         ANTICHTANOTRYPSIN         11.61         4.3.35         51.65         88.66         3.6           ANTICHTAJSTORS         Mont FLJ35030, highly similar to ALPHA-1.         43.33         16         51.65         88.61         3.6           ANTICHTAJSTOR         Bena protecting the rest properties of multiporties of multiporties of multiporties of multiporties of multiporties         2.06         7         2.65         11         11.31.4         82.99         6.9         3.3           CINA FLJ35030, highly similar to score and multiporties         5.26         1         10.13.2         88.9         10.13.2         88.9         6.8         3.3           Plasma protense C1 inhibitor         33.17         15         5.2         4.31.5         8.8         3.3         7         9.8         2.2         2.4         7         9.3         2.3         <	IPI00555812	Vitamin D-binding protein	42.62	17	62.88	76.48	5.7	0.006000	
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	IP100022426	Protein AMBP	17.61	4	78.76	46.73	2.4	0.007000	
ANTICHYMOTRYPSIN         727         2         25         1         13,14         8,29         69           OINA FLJS0830, highly similar to complement of precursor         2,59         1         101,32         8,39         63           Complement of precursor         5,29         1         101,32         8,39         63           ENV polyprotein (coat polyprotein) family protein         2,06         7         9085         8,3         3           Plasma protease (1) inhibitor         2,06         7         33,17         15         8491         8,34         7           Plasma protease (1) inhibitor         33,17         15         8,491         8,53         3,7           Plasma protease (1)         21,15         5,4,39         7,94         3,7           Putative uncharacterized protein L         3,31,7         15         8,47         7           Putative uncharacterized protein L         3,17         1,5         8,47         7           ONA FLJS1265, moderately similar to         5,2         4,315         8,53         3,1           CRUUDPLASMIN         5,2         2,44         8,53         3,1         8,53         3,1           CRULDPLASMIN         CRULLOPLASMIN         3,1,15         8,6	IPI00550991	cDNA FLJ35730 fis. clone TESTI2003131. highly similar to ALPHA-1-	43.53	16	51.65	68.56	3.6	0.008000	
$ \begin{array}{llllllllllllllllllllllllllllllllllll$		ANTICHYMOTRYPSIN							
Complement component 6 precursor $2.65$ 1 $137.14$ $8.289$ $6.9$ ENV polyprotein (cont polyprotein) family protein $5.29$ 1 $101.32$ $85.96$ $8.3$ Putative uncharacterized protein F2 $5.29$ 1 $101.32$ $85.96$ $8.3$ Putative uncharacterized protein F2 $5.17$ $5.18$ $9.018$ $85.32$ $54.33$ Putative uncharacterized protein F2 $5.17$ $5.18$ $8.9$ $70.48$ $3.7$ Beta-2-glycoprotein 1 $31.75$ $6$ $57.7$ $54.38$ $2.2$ ONA FLJ51265, moderately similar to $5.22$ $2.44.31$ $8.87.3$ $3.9$ ONA FLJ51265, moderately similar to $5.77$ $54.38$ $2.43$ $3.9$ ONA FLJ51265, moderately similar to $5.13$ $3.17$ $3.17$ $3.17$ $3.88$ $2.43$ CERULOPLASMIT $31.75$ $54.87$ $4$ $4.93$ $8.77$ $54.38$ $2.3$ CIBAR $6.00$ $7.12$ $8.77$ $8.77$	IP100908876	cDNA FLJ50830. highly similar to Serum albumin	7.27	2	126.5	89.61	13	000600.0	
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	IPI00879709	Complement component 6 precursor	2.65		137.14	82.89	6.9	0.009000	
Plasma protectized protein $P_2$ 20.6750.856.833.17Plasma protexer (2 d) protein $P_2$ Plasma protexer (2 d) protein $P_2$ 33.171584.9183.547Putative uncharacterized protein $P_2$ DNA FLJ37071 fis, clone CTONG200958, highly similar to33.171584.9183.547Plasma protexe (1 inhibit)DNA FLJ37071 fis, clone CTONG200958, highly similar to33.171584.9183.547Beta-zyroprotein 131.7565.775.4.382.2CERULOPLASMIN5.243.1554.382.3CUNA FLJ51265, moderately similar to Beta-2-glycoprotein 131.75657.775.3.852.3CUNA FLJ51265, moderately similar to Beta-2-glycoprotein 131.75657.775.3.852.3CUNA FLJ51265, moderately similar to Beta-2-glycoprotein 131.75657.775.3.852.3CUNA FLJ51265, moderately similar to Beta-2-glycoprotein 121.8386.473.174.2CUNA functionComplement component C3, partial3.0124.2.316.8533.1Cundement component C3Data protein9.3514.2.316.8533.1Complement component C3Data protein0.1524.4.12.4Complement component C3E.4.99E.4.2324.4.232.4Complement component C3E.4.99E.4.9924.4.12.4Complement component C3E.4.99E.4.232.4 <td< td=""><td>IPI00884751</td><td>ENV nolvnrotein (coat nolvnrotein) family nrotein</td><td>5 29</td><td></td><td>101 32</td><td>85.96</td><td>~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~</td><td>0006000</td><td></td></td<>	IPI00884751	ENV nolvnrotein (coat nolvnrotein) family nrotein	5 29		101 32	85.96	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	0006000	
Putative uncharacterized protein ALB $33.17$ $15$ $84.91$ $85.54$ $7$ Putative uncharacterized protein P2Putative uncharacterized protein P2 $16.67$ $3$ $38.9$ $70.48$ $37$ Putative uncharacterized protein P2Beta-2-glycoprotein 1 $32.75$ $8$ $50.08$ $83.28$ $224$ Beta-2-glycoprotein 1 $31.75$ $6$ $57.7$ $53.85$ $223$ CERULOPLASMNCERULOPLASMN $52$ $44.15$ $49$ $81.71$ $49$ CURNA FLJ51265, moderately similar to Beta-2-glycoprotein 1 $31.75$ $6$ $57.7$ $53.85$ $23$ CURNA fruction $52$ $2$ $43.17$ $31.75$ $6$ $57.7$ $53.85$ $23$ CURNA domain-containing protein 4 $21.83$ $8$ $64.87$ $81.71$ $49$ Similar to complement component C3, partial $51.64$ $42.31$ $68.53$ $31.1$ Solut portein $1.56$ $1$ $42.31$ $68.53$ $31.1$ Solut protein $1.56$ $1$ $42.31$ $68.57$ $53.85$ $53$ Solut portein $1.56$ $1$ $25.44$ $26.49$ $44.607$ $27.7$ Solut protein $1.56$ $1$ $2.54$ $60.44$ $25.7$ Complement factor $1$ $41.29$ $10$ $92.7$ $88.71$ $24.9$ Solut protein $7$ $88.77$ $66.04$ $25.7$ $55.67$ $56.9$ $27.4$ Complement factor $1.816$ $67.9$ $92.4$ $4.61$ $1.7$	1PI00291866	Plasma nrotease (1 inhibitor	20.6	- 1-	50.85	68		0.009000	
Putative uncharacterized protein F2 $16.67$ $32$ $38.9$ $70.48$ $3.7$ Putative uncharacterized protein F2Beta-2-glycoprotein I $32.75$ $8$ $50.08$ $58.28$ $24$ Beta-2-glycoprotein I $5.2$ $21.35$ $6$ $57.7$ $53.82$ $22$ CENUL PLASMIN $5.2$ $31.75$ $6$ $57.7$ $53.82$ $22$ CENUL PLASMIN $5.2$ $31.75$ $6$ $57.7$ $53.82$ $22$ CENUL PLASMIN $5.2$ $21.83$ $8$ $64.87$ $81.71$ $49$ CENUL PLASMIN $5.2$ $21.83$ $8$ $64.87$ $81.71$ $49$ CENUL PLASMIN $5.2$ $21.83$ $8$ $64.87$ $81.71$ $49$ CENUL PLASMIN $21.83$ $8$ $64.87$ $81.71$ $49$ CUUSterin $21.83$ $8$ $64.87$ $81.71$ $49$ CINSA domain-containing protein $21.83$ $8$ $64.87$ $81.71$ $49$ Sinilar to complement component C3, partial $3.01$ $21.83$ $8$ $64.87$ $81.71$ $49$ I (k kba protein $26.49$ $41.29$ $10.67$ $92.74$ $41.29$ $20.49$ $55.59$ $24$ Alpha-1-acid glycoprotein $16.83$ $12.649$ $41.29$ $12.649$ $52.49$ $56.93.61$ $27.44$ Complement factor $00.927$ $14.129$ $10.927$ $88.72$ $44.129$ $52.49$ $56.93.61$ $57.49$ $56.69$ $27.49$ Alpha-1-acid glycoprotein $20$	IPI00022434	Putative uncharacterized protein ALB	33.17	. 1	84 91	83 54	1	0006000	
Beta-2-elycoprotein 1       37.75       8       50.08       58.28       24         CERULOPLASMIN       5.2       43.15       54.38       22         CERULOPLASMIN       5.2       2       43.15       54.38       22         CERULOPLASMIN       5.2       2       43.15       54.38       22         CINA FLJ37971 fis, clone CTONG200958, highly similar to       5.2       43.15       54.38       2.2         CUsterin       21.155       6       57.7       53.85       2.3         CUUsterin       21.83       8       6.487       81.71       4.9         Clusterin       21.83       8       6.487       81.71       4.9         Standardy similar to complement C3, partial       3.01       2       9.917       85.98       6.6         Standardy storein       3.01       2       9.917       85.98       6.6       2.4         Standardy storein       3.01       2       4       46.87       101.59       2.4         Standardy domain-component C3, partial       3.01       2       4       46.69       8.74       2.4         Ok ba protein       Alburater and component C3       5       5       4       2.5       5	TPI00877967	Putative uncharacterized protein F2	16.67	, rr	38.9	70.48	3.7	0006000	
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	IPI00298828	Beta-2-elvconrotein 1	32.75	×	50.08	58.28	2.4	0.010000	
CERULOPLASMINCERULOPLASMINCDNA FLJ51265, moderately similar to Beta-2-glycoprotein 1 $31.75$ $6$ $57.7$ $53.85$ $2.3$ ClusterinClusterin $21.83$ $8$ $64.87$ $81.71$ $4.9$ ClusterinClusterin $21.83$ $8$ $64.87$ $81.71$ $4.9$ ClusterinClusterin $21.83$ $8$ $64.87$ $81.71$ $4.9$ Clusterin $1.56$ $1$ $4.231$ $65.53$ $3.1$ Similar to complement component C3, partial $3.01$ $2$ $4$ $66.83$ $3.1$ 16 KDa protein $9.35$ $2.35$ $1$ $46.68$ $101.59$ $22.4$ 20 kDa protein $20.4Da$ $9.27$ $4$ $6.69$ $89.2$ $4$ 20 kDa protein $6.66$ $37.12$ $58.44$ $2.7$ 20 kDa protein $14.129$ $10$ $92.77$ $78.72$ $4$ 20 kDa protein $7$ $8.92$ $4.66.9$ $89.51$ $5.8$ 20 complement factor 1 $14.129$ $10$ $92.77$ $78.72$ $4$ Histidine-rich glycoprotein $7$ $8.48$ $6.6.9$ $89.51$ $5.8$ 10 stative undwaracterized protein $7$ $14.12$ $14.12$ $14.15$ $14.11$ 11 studive undwaracterized protein $7$ $14.12$ $14.15$ $14.12$ $24.44$ 20 kDa protein $78.26$ $81.96$ $57.66$ $81.96$ $57.66$ $81.96$ 21 kDa protein $78.26$ $14.46$ $78.26$ $81.96$ $74.36$ <	IPI00794184	cDNA FLI37971 fis clone CTONG2009958 highly similar to	5.2	) <i>C</i>	43.15	54 38	2.2	0.010000	
$ \begin{array}{llllllllllllllllllllllllllllllllllll$		CERTILOPLASMIN	i i	1		2	i	000010:0	
ClusterinClusterin $21.83$ $8$ $64.87$ $81.71$ $4.9$ GRAM domain-containing protein 4 $1.56$ $1$ $42.31$ $68.53$ $3.11$ similar to complement component C3, partial $3.01$ $2$ $9.17$ $85.98$ $6.6$ $16$ kDa protein $9.35$ $1$ $46.68$ $101.59$ $22.4$ $16$ kDa protein $9.35$ $1$ $46.68$ $101.59$ $22.4$ $20$ kDa protein $2.64.9$ $4$ $68.87$ $6.04$ $2.5$ $20$ kDa protein $2.64.9$ $4$ $68.87$ $66.04$ $2.5$ $20$ kDa protein $1.29$ $10$ $9.27$ $78.72$ $4$ $20$ kDa protein $41.29$ $10$ $92.7$ $78.74$ $2.4$ $20$ complement component C9 $8.92$ $4$ $66.9$ $2.7$ $4$ $14$ kDiffine-rich glycoprotein $8.92$ $4$ $66.9$ $2.7$ $4$ $16$ kDa protein $7.45$ $8.743$ $5.3$ $5.3$ $5.3$ $16$ kDa protein $14.15$ $14.15$ $4.6$ $11$ $8.6.52$ $93.61$ $6.7$ $16$ kDa protein $7.87$ $4.61$ $1$ $8.6.52$ $93.61$ $6.7$ $5.76$ $81.96$ $5.7$ $16$ kDa protein $14.15$ $14.15$ $8.743$ $5.76$ $81.96$ $5.7$ $5.66$ $81.96$ $5.7$ $16$ kDa protein $12.5$ kDa protein $7.45$ $7.43$ $5.76$ $81.96$ $5.76$ $81.96$ $5.74$ $16$ kDa protein <td>IPI00910625</td> <td>oderately similar to</td> <td>31.75</td> <td>9</td> <td>57.7</td> <td>53.85</td> <td>2.3</td> <td>0.010000</td> <td></td>	IPI00910625	oderately similar to	31.75	9	57.7	53.85	2.3	0.010000	
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	IP100291262		21.83	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	64.87	81.71	4.9	0.010000	
similar to complement component C3, partial $3.01$ $2$ $9.17$ $85.98$ $6.6$ 16 kDa protein16 kDa protein $9.35$ 1 $46.68$ $101.59$ $22.4$ 20 kDa protein $20$ kDa protein $9.35$ 1 $46.68$ $101.59$ $22.4$ 20 kDa protein $20$ kDa protein $2.0$ kDa protein $9.35$ $1$ $46.68$ $101.59$ $22.4$ 20 kDa protein $20$ kDa protein $20$ kDa protein $26.49$ $4$ $68.87$ $66.04$ $2.5$ Alpha-1-acid glycoprotein $41.29$ $10$ $92.7$ $78.72$ $4$ Complement factor 1 $8.92$ $4$ $66.9$ $89.51$ $5.8$ Complement factor 1 $8.92$ $4.61$ $1$ $43.16$ $87.43$ $5.3$ Putative uncharacterized protein ENSP00000374858 (Fragment) $14.15$ $1$ $43.16$ $87.43$ $5.3$ Putative uncharacterized protein ENSP00000374858 (Fragment) $14.15$ $1$ $43.16$ $87.43$ $5.3$ Putative uncharacterized protein ENSP00000374858 (Fragment) $14.15$ $1$ $43.16$ $87.43$ $5.3$ Putative uncharacterized protein ENSP00000374858 (Fragment) $5.76$ $1$ $86.52$ $99.61$ $6.7$ Putative uncharacterized protein ENSP00000374988 (Fragment) $5.76$ $1$ $65.69$ $2.74$ $6.743$ $5.743$ $5.749$ $65.69$ $2.749$ Putative uncharacterized protein ENSP00000374988 (Fragment) $5.76$ $1$ $6.705$ $67.19$ $6.743$ $5.743$ <t< td=""><td>IPI00019690</td><td>GRAM domain-containing protein 4</td><td>1.56</td><td>1</td><td>42.31</td><td>68.53</td><td>3.1</td><td>0.010000</td><td></td></t<>	IPI00019690	GRAM domain-containing protein 4	1.56	1	42.31	68.53	3.1	0.010000	
16 kDa protein9.35146.68101.5922.420 kDa protein20 kDa protein20 kDa protein26.49466.042.520 kDa protein20 kDa protein26.49468.8766.042.5Alpha-1-acid glycoprotein 16.26383.1258.442.4Complement factor 18.9246.6989.515.8Complement factor 118.4865.692.7Histidine-rick glycoprotein18.4865.692.7Insulin-like growth factor-binding protein 718.4865.246.7Putative uncharacterized protein FNSP0000374858 (Fragment)14.15143.1687.435.3Putative uncharacterized protein ENSP0000374858 (Fragment)5.76155.6681.963.7Q kDa protein734.821361.8391.494.4Putative uncharacterized protein ENSP0000374988 (Fragment)5.76155.6681.963.7A tative uncharacterized protein ENSP0000374988 (Fragment)5.76155.6681.963.7A tative uncharacterized protein ENSP0000374988 (Fragment)5.76155.6681.963.7A tative uncharacterized protein734.821361.6791.24.4A tative uncharacterized protein5.76155.6681.965.74.4A tative uncharacterized protein5.761786.5291.494.4A tative unch	IPI00887739	similar to complement component C3, partial	3.01	2	99.17	85.98	6.6	0.010000	
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	IP100556036	16 kDa protein	9.35	1	46.68	101.59	22.4	0.020000	
Alpha-1-acid glycoprotein 1 $41.29$ $10$ $92.7$ $78.72$ $4$ Complement factor 1Complement factor 1 $6.26$ $3$ $83.12$ $58.44$ $2.4$ Complement factor 1Complement factor 1 $6.26$ $3$ $83.12$ $58.44$ $2.4$ Complement factor 1 $8.92$ $4$ $6.9$ $89.51$ $5.8$ $2.7$ Histidime-rick glycoprotein $18.48$ $6$ $5.49$ $65.69$ $2.7$ Insulin-like growth factor-binding protein 7 $4.61$ $1$ $43.16$ $87.43$ $5.3$ Putative uncharacterized protein ENSP0000374858 (Fragment) $14.15$ $1$ $43.16$ $87.43$ $5.3$ Putative uncharacterized protein ENSP0000374958 (Fragment) $5.76$ $1$ $86.52$ $99.61$ $6.7$ Putative uncharacterized protein $5.76$ $1$ $86.52$ $91.49$ $4.4$ $2N kD protein6.94281.963.742 kDa protein6.94281.963.742 kDa protein6.94281.966.742 kDa protein7.861460.6791.24.342 kDa protein7.861460.6791.204.442 kDa protein7.861460.6791.24.342 kDa protein7.861460.6791.24.342 kDa protein7.861460.6791.24.342 kDa protein7.86$	IPI00940791	20 kDa protein	26.49	4	68.87	66.04	2.5	0.020000	
Complement component C9       6.26       3       83.12       58.44       2.4         Complement factor I       8.92       4       66.9       89.51       5.8         Complement factor I       8.92       4       66.9       89.51       5.8         Complement factor I       8.92       4.61       1       4.61       5.69       2.7         Insulin-like growth factor-binding protein 7       4.61       1       14.15       1       4.31.6       87.43       5.3         Putative uncharacterized protein ENSP0000374988 (Fragment)       14.15       1       8.6.52       93.61       6.7         24 kDa protein       6.9       81.96       3.7       14.15       1       86.52       93.61       6.7         20NA FLJ56822, highly similar to Alpha-2-HS-glycoprotein       6.94       2       2       82.08       90.01       4.1         Haptoglebin       81.96       3.786       1       55.66       81.96       3.7       14.15         Haptoglebin       81.81       6.94       2       2       82.08       90.01       4.1         Haptoglebin       81.94       3.786       14       60.9       91.29       4.3       10.01       4.1	IP100022429	Alpha-1-acid glycoprotein 1	41.29	10	92.7	78.72	4	0.020000	
Complement factor I       8.92       4       66.9       89.51       5.8         Histidine-rich glycoprotein       18.48       6       52.49       65.69       2.7         Insulin-like growth factor-binding protein 7       4.61       1       4.3.16       87.43       5.3         Putative uncharacterized protein ENSP0000374988 (Fragment)       14.15       1       8.52       93.61       6.7         Putative uncharacterized protein ENSP0000374988 (Fragment)       14.15       1       85.52       93.61       6.7         Putative uncharacterized protein ENSP0000374988 (Fragment)       5.76       1       55.66       81.96       3.7         42 kDa protein       SNA FLJ56822, highly similar to Alpha-2-HS-glycoprotein       6.94       2       86.52       91.49       4.4         Raptoglobin       37.86       14       60.67       91.2       4.3         Inter-alpha-trypsin inhibitor heavy chain H2       3.59       2       67.05       67.19       2.4         Lysozyme C       35.14       3       99.3       100.08       6.8	IP100022395	Complement component C9	6.26	ŝ	83.12	58.44	2.4	0.020000	
Histidine-rich glycoprotein       18.48       6       52.49       65.69       2.7         Insulin-like growth factor-binding protein 7       4.61       1       4.51.6       87.43       5.3         Putative uncharacterized protein ENSP0000374858 (Fragment)       14.15       1       86.52       93.61       6.7         Putative uncharacterized protein ENSP00000374988 (Fragment)       14.15       1       86.52       93.61       6.7         Quartive uncharacterized protein ENSP00000374988 (Fragment)       5.76       1       85.56       81.96       3.7         42 kDa protein       SNA FLJ56822, highly similar to Alpha-2-HS-glycoprotein       6.94       2       82.08       90.01       4.1         Haptoglobin       37.86       14       6.067       91.2       4.3         Inter-alpha-trypsin inhibitor heavy chain H2       3.59       2       67.05       67.19       2.4         Lysozyme C       35.14       3       99.3       100.08       6.8	IPI00291867	Complement factor I	8.92	4	60.9	89.51	5.8	0.020000	
Insulin-like growth factor-binding protein 7       4.61       1       43.16       87.43       5.3         Putative uncharacterized protein ENSP0000374858 (Fragment)       14.15       1       86.52       93.61       6.7         Putative uncharacterized protein ENSP0000374958 (Fragment)       5.76       1       85.66       81.96       3.7         Putative uncharacterized protein ENSP0000374958 (Fragment)       5.76       1       55.66       81.96       3.7         42 kDa protein       34.82       13       61.83       91.49       4.4         42 kDa protein       6.94       2       82.08       90.01       4.1         Haptoglobin       37.86       14       60.67       91.2       4.3         Inter-alpha-trypsin inhibitor heavy chain H2       3.59       2       67.05       67.19       2.4         Lysozyme C       35.14       3       99.3       100.08       6.8	IPI00022371	Histidine-rich glycoprotein	18.48	9	52.49	65.69	2.7	0.020000	
Putative uncharacterized protein ENSP0000374858 (Fragment)       14.15       1       86.52       93.61       6.7         Putative uncharacterized protein ENSP00000374988 (Fragment)       5.76       1       55.66       81.96       3.7         Putative uncharacterized protein ENSP00000374988 (Fragment)       5.76       1       55.66       81.96       3.7         42 kDa protein       34.82       13       61.83       91.49       4.4         cDNA FLJ56822, highly similar to Alpha-2-HS-glycoprotein       6.94       2       82.08       90.01       4.1         Haptoglobin       37.86       14       60.67       91.2       4.3       11         Inter-alpha-trypsin inhibitor heavy chain H2       3.59       2       67.05       67.19       2.4       14         Lysozyme C       35.14       3       99.3       100.08       6.8       14	IP100016915	Insulin-like growth factor-binding protein 7	4.61	1	43.16	87.43	5.3	0.020000	
Putative uncharacterized protein ENSP0000374988 (Fragment)       5.76       1       55.66       81.96       3.7         42 kDa protein       34.82       13       61.83       91.49       4.4         42 kDa protein       34.82       13       61.83       91.49       4.4         6 DNA FLJ56822, highly similar to Alpha-2-HS-glycoprotein       6.94       2       82.08       90.01       4.1         Haptoglobin       37.86       14       60.67       91.2       4.3         Inter-alpha-trypsin inhibitor heavy chain H2       3.59       2       67.05       67.19       2.4         Lysozyme C       35.14       3       99.3       100.08       6.8	IPI00830047	Putative uncharacterized protein ENSP00000374858 (Fragment)	14.15	1	86.52	93.61	6.7	0.020000	
42 kDa protein       34.82       13       61.83       91.49       4.4         cDNA FLJ56822, highly similar to Alpha-2-HS-glycoprotein       6.94       2       82.08       90.01       4.1         Haptoglobin       37.86       14       60.67       91.2       4.3         Inter-alpha-trypsin inhibitor heavy chain H2       3.59       2       67.05       67.19       2.4         Lysozyme C       35.14       3       99.3       100.08       6.8	IP100736860	Putative uncharacterized protein ENSP00000374988 (Fragment)	5.76	1	55.66	81.96	3.7	0.020000	
cDNA FLJ56822, highly similar to Alpha-2-HS-glycoprotein       6.94       2       82.08       90.01       4.1         Haptoglobin       37,86       14       60.67       91.2       4.3         Inter-alpha-trypsin inhibitor heavy chain H2       3.59       2       67.05       67.19       2.4         Lysozyme C       35.14       3       99.3       100.08       6.8	IPI00942787	42 kDa protein	34.82	13	61.83	91.49	4.4	0.030000	
Haptoglobin         37.86         14         60.67         91.2         4.3           Inter-alpha-trypsin inhibitor heavy chain H2         3.59         2         67.05         67.19         2.4           Lysozyme C         35.14         3         99.3         100.08         6.8	IP100922262	cDNA FLJ56822, highly similar to Alpha-2-HS-glycoprotein	6.94	7	82.08	90.01	4.1	0.030000	
Inter-alpha-trypsin inhibitor heavy chain H2         3.59         2         67.05         67.19         2.4           Lysozyme C         35.14         3         99.3         100.08         6.8	IPI00641737	Haptoglobin	37.86	14	60.67	91.2	4.3	0.030000	
Lysozyme C 35.14 3 99.3 100.08 6.8	IPI00305461	Inter-alpha-trypsin inhibitor heavy chain H2	3.59	7	67.05	67.19	2.4	0.030000	
	IP100019038	Lvsozvme C	35.14	С	99.3	100.08	6.8	0.030000	

© 2011 Molecular Vision

	TABLE 2	TABLE 2. CONTINUED.						
Protein ID	Protein name	Protein	Number of	CV (%)	CV (%)	Fold	p-value	Plasma
		coverage	unique	normal	shunt	change in	(shunt	protein
		(%)	sedneuces			shunt	Versus	
1P100855916	Transthuratin	55 43	1	56.66	51.02	pauents 1 9		
IPI00910636	cDNA FLJ53848, highly similar to Inter-alpha-trypsin inhibitor heavy	2.76		105.83	80.27	3.2	0.040000	
	chain H2		c			0		
IP100032293	Cystatin-C	11.04	710	51.2	60.84	77	0.040000	
IP100426060	Putative uncharacterized protein DKF Zp686J11235 (Fragment)	24.11	~ ~	10.00	10.41	4 V 4	0.040000	
214012101711 221202001010	DOUTIDASE DNIA ET 15.471 bizelty similar to Comulation Of a subsomment	61.6 201		00.7C1	90.90 100 52	C.2	0000200	
1F100290103 1P100022418	CDIAR FL/24471, inginy summa to Comprement C11 subcomponent Fibronectin	163	- (	20.2 49 85	CC-001	5 ¢	0.050000	
11100022418 11100478493	I 1010000000 Hantoolohin isoform 2 nranronrotein	24.01	4 C	64.09	06.65 06.65	0.7 C T	0.05000	
IPI00431645	Haprogroun isotonii z preproprotein HP nrotein	25.62	2 9	72.49	101 65	4.9	0.050000	
IPI00910432	cDNA FL J57921. highly similar to Apolipoprotein D	10.94	~ —	32.12	115.55	6.7	0.060000	
IPI00156171	Ectonucleotide pyrophosphatase/phosphodiesterase family member 2	4.06	0	154.37	118.59	9.6	0.060000	
IPI00026199	Glutathione peroxidase 3	29.2	9	62.58	52.9	1.9	0.060000	
IP100292150	Latent-transforming growth factor beta-binding protein 2	1.04	1	35.63	129.41	22.1	0.060000	
IP100002678	Opticin	14.46	2	44.87	57.55	1.8	0.060000	
IP100852577	HCG2040025	33.02	7	79.85	92.66	3.2	0.070000	
IP100021000	Osteopontin	10.19	7	73.71	115.05	6.2	0.070000	
IP100514159	Inter-alpha (Globulin) inhibitor H2	8.02	1	61.82	59.15	1.8	0.090000	
IP100029863	55 kDa protein (Alpha-2-antiplasmin precursor)	8.69	7	55.95	78.97	-1.8	0.100000	
IP100002147	Chitinase-3-like protein 1	9.92	7	56.83	128.11	4.3	0.100000	
IP100009650	Lipocalin-1	6.25	1	66.59	61.11	1.8	0.100000	
IPI00844156	SERPINC1 protein	3.86	1	77.33	80.74	2.3	0.100000	
IPI00383164	SNC66 protein	19.72	7	64.5	79.48	2.1	0.100000	
IPI00794403	23 kDa protein	17.82	ю	80.99	159.25	9.8	0.200000	
IP100922298	cDNA FLJ51445, highly similar to AMBP protein	7.04	1	64.26	81.95	7	0.200000	
IP100022431	cDNA FLJ55606, highly similar to Alpha-2-HS-glycoprotein	13.39	4	49.95	144.5	5.1	0.200000	
IP100029739	Complement factor H	1.46	1	48.36	116.78	2.6	0.200000	
IPI00021891	Fibrinogen gamma chain	7.51	7	86.57	136.01	3.5	0.200000	
IPI00292530	Inter-alpha-trypsin inhibitor heavy chain H1	2.09	-	66.21	40.03	-1.7	0.200000	
IP100020986		16.86	4 (	72.95	148.83 70.20	7.5 1	0.20000	
C202200141	Prostaglandin DZ synthase 21 kDa	14./3	7	C0.20	70.58		0.200000	
2 CU8 COUU141	Putative uncharacterized protein CISD	40.8 44 A		40.03 77 77	C7.61	1./	00000000	
IF1006/7923 IPI00218732	r utative unchatacterized protein dent invez Serium paravyonase/anylesterase 1	0.44 6.2	1 -	41.72	55 A	0.1 . 2	0.200000	
IP100006662	Anolinonrotein D	20.11	- (1)	201.07	113.63	2.7	0.300000	
IP100165972	Complement factor D preproprotein	15	7	63.48	59	1.5	0.300000	
IP100930442	Putative uncharacterized protein DKFZp686M24218	5.67	1	99.15	71.25	1.7	0.300000	
IP100935408	CFI protein	4.24	1	81.47	78.69	1.3	0.400000	
IP100022417	Leucine-rich alpha-2-glycoprotein	29.97	5	59.22	42.95	1.2	0.400000	
IP100334282	Protein FAM3C	7.05	1	38.27	61.04	-1.1	0.500000	
IP100012503	Proactivator polypeptide	2.86	1	262.28	79.65	1.8	0.600000	
IPI00807428	Putative uncharacterized protein	22.98	3	168.41	135.85	2.1	0.600000	
IPI00011229	Cathepsin D	8.5	2	106.86	100.28	-1.5	0.700000	
IPI00423460	Putative uncharacterized protein DKFZp686G21220 (Fragment)	9.88	ŝ	104.19	116.55	1.6	0.700000	
IP100022337	Retinol-binding protein 3	5.93	ε	71.53	69.31	1.1	0.800000	
IPI00301579	cDNA FLJ59142, highly similar to Epididymal secretory protein E1	7.96	]	39.81	61.76	1.2	0.900000	
Differen	Differentially expressed proteins detected using stringent filtering criteria are highlighted in bold	highlighted in	bold.					

© 2011 Molecular Vision

#### Molecular Vision 2011; 17:1891-1900 < http://www.molvis.org/molvis/v17/a206>

role in glaucoma and corneal endothelial damage needs further evaluation.

Increased expression of apolipoprotein A-I (fold change, 6.4; p=0.0004) and A-II (fold change, 18.4; p=0.0002) was observed in this study. Apo A-1 and – II, by virtue of their association with high density lipoprotein (HDL), have anti-inflammatory properties [51]. However, its specific role in glaucoma and corneal endothelial damage is unclear and requires further investigation.

Fibronectin, an extracellular matrix glycoprotein, was increased sixfold in this study compared to normal controls (p=0.0003). This suggests disruption of the blood aqueous barrier that occurs in eyes with a glaucoma shunt device. Vesaluoma et al. [30] have demonstrated increased expression of this protein in eyes with pseudoexfoliation glaucoma. Increased fibronectin can transform TM cells and decrease the breakdown of extracellular matrix material, allowing excess to accumulate. This could ultimately reduce trabecular outflow and raise IOP.

RIG-like 7–1 constitute a family of pattern recognition receptors (PRRs). They mediate the initial sensing of microbial and endogenous danger-associated molecules that are released by tissue damage. By activating transcription of inflammatory genes they are known to control the immediate innate immune response as well as the subsequent adaptive immune response [52]. Increased levels of PRR suggests an alteration in the immunologic milieu of the AH secondary to a breach in the blood aqueous barrier.

Beta-2 microglobulin is a protein associated with major histocompatibility complex class I antigens and has value as a marker for immunologic monitoring with increased levels associated with renal and cardiac allograft rejection [53,54]. Elevated levels as seen in this study (fold change, 5.7; p=0.0002) suggest a potential role for this protein as a biomarker of increased immune mediated corneal endothelial damage in eyes with a glaucoma shunt device.

Based on the protein profile detected in this study we have hypothesized the likely mechanisms underlying corneal endothelial damage in eyes with a shunt device as well as new insights into glaucoma pathophysiology. Glaucoma per se also causes corneal endothelial damage and in the presence of glaucoma shunt device there is likely to be an exaggerated stress response leading to corneal endothelial damage and endothelial failure. This has important implications especially in the setting of corneal transplants. Corneal grafts have significantly poor long-term survival in the presence of a shunt device and future work should be targeted at identifying the specific role for these proteins so that they could potentially serve as therapeutic targets to improve graft outcomes.

This study has several strengths that need to be highlighted. The AH samples were not pooled but analyzed individually to determine proteins associated with a shunt device. We used conservative criteria for determining which proteins were differentially expressed between groups and were able to identify highly significant proteins with a large fold change compared to normals. It has been shown that the proteomic profile in glaucoma patients can vary depending on the severity of visual field defects [22]. The study patients had advanced glaucoma and this could partly explain the identification of novel proteins. The limitations of this study include the small sample size, although it is comparable to previous studies evaluating AH in eyes with glaucoma [21, 22]. A useful control group would have been glaucoma patients without a shunt device who were undergoing intraocular surgery. A proteomic study with glaucoma as a control group is currently ongoing and should provide more insight into the pathogenic mechanism of corneal endothelial damage specific to glaucoma shunt device. This study reports on differential expression of proteins compared to normal controls but does not provide absolute quantitative data on protein levels.

Lastly, the majority of study patients had an Ahmed glaucoma shunt, which is a valved implant designed to prevent retrograde flow of fluid from the filtering bleb into the eye, so it would be interesting to determine the mechanism of increased inflammation and/or immunologic alterations seen in these eyes. Future work should be directed at evaluating the AH proteomic expression in the presence of valved and nonvalved glaucoma shunts to shed light on the possible mechanisms of corneal endothelial damage with different types of shunts.

*Conclusion:* We demonstrated significantly altered expression of 13 proteins in AH of eyes with a glaucoma shunt device. Many of these proteins play a role in oxidative and apoptotic damage. The findings of this study seem to suggest similar mechanisms underlying both glaucoma and corneal endothelial damage. Future work should be targeted at identifying aqueous proteins that could potentially serve as markers for corneal endothelial damage in eyes with glaucoma shunt device.

## ACKNOWLEDGMENTS

This study was supported by a grant from the Cornea Research Foundation of America. Authors have no commercial interest in the subject matter discussed in the manuscript. The data from this manuscript has not been presented at meetings/ conferences.

#### REFERENCES

- Wilson SE, Kaufman HE. Graft failure after penetrating keratoplasty. Surv Ophthalmol 1990; 34:325-56. [PMID: 2183380]
- Thompson RW Jr, Price MO, Bowers PJ, Price FW Jr. Longterm graft survival after penetrating keratoplasty. Ophthalmology 2003; 110:1396-402. [PMID: 12867398]
- 3. Ayyala RS. Penetrating keratoplasty and glaucoma. Surv Ophthalmol 2000; 45:91-105. [PMID: 11033036]

Molecular Vision 2011; 17:1891-1900 < http://www.molvis.org/molvis/v17/a206>

- Seitz B, Langenbucher A, Nguyen NX, Kuchle M, Naumann GO. Long-term follow-up of intraocular pressure after penetrating keratoplasty for keratoconus and Fuchs' dystrophy: comparison of mechanical and Excimer laser trephination. Cornea 2002; 21:368-73. [PMID: 11973385]
- Greenlee EC, Kwon YH. Graft failure: III. Glaucoma escalation after penetrating keratoplasty. Int Ophthalmol 2008; 28:191-207. [PMID: 18431550]
- Williams KA, Lowe M, Bartlett C, Kelly TL, Coster DJ. Risk factors for human corneal graft failure within the Australian corneal graft registry. Transplantation 2008; 86:1720-4. [PMID: 19104411]
- Sugar A, Tanner JP, Dontchev M, Tennant B, Schultze RL, Dunn SP, Lindquist TD, Gal RL, Beck RW, Kollman C, Mannis MJ, Holland EJ. Recipient risk factors for graft failure in the cornea donor study. Ophthalmology 2009; 116:1023-8. [PMID: 19395036]
- Kwon YH, Taylor JM, Hong S, Honkanen RA, Zimmerman MB, Alward WL, Sutphin JE. Long-term results of eyes with penetrating keratoplasty and glaucoma drainage tube implant. Ophthalmology 2001; 108:272-8. [PMID: 11158798]
- Alvarenga LS, Mannis MJ, Brandt JD, Lee WB, Schwab IR, Lim MC. The long-term results of keratoplasty in eyes with a glaucoma drainage device. Am J Ophthalmol 2004; 138:200-5. [PMID: 15289127]
- Al-Torbak A. Graft survival and glaucoma outcome after simultaneous penetrating keratoplasty and ahmed glaucoma valve implant. Cornea 2003; 22:194-7. [PMID: 12658081]
- Price MO, Fairchild KM, Price DA, Price FW Jr. Descemet's Stripping Endothelial Keratoplasty Five-Year Graft Survival and Endothelial Cell Loss. Ophthalmology 2011; 118:725-9. [PMID: 21035862]
- Kim CS, Yim JH, Lee EK, Lee NH. Changes in corneal endothelial cell density and morphology after Ahmed glaucoma valve implantation during the first year of follow up. Clin Experiment Ophthalmol 2008; 36:142-7. [PMID: 18352870]
- Kirkness CM. Penetrating keratoplasty, glaucoma and silicone drainage tubing. Dev Ophthalmol 1987; 14:161-5. [PMID: 3308553]
- McDonnell PJ, Robin JB, Schanzlin DJ, Minckler D, Baerveldt G, Smith RE, Heuer D. Molteno implant for control of glaucoma in eyes after penetrating keratoplasty. Ophthalmology 1988; 95:364-9. [PMID: 3050684]
- Topouzis F, Coleman AL, Choplin N, Bethlem MM, Hill R, Yu F, Panek WC, Wilson MR. Follow-up of the original cohort with the Ahmed glaucoma valve implant. Am J Ophthalmol 1999; 128:198-204. [PMID: 10458176]
- Funding M, Vorum H, Honore B, Nexo E, Ehlers N. Proteomic analysis of aqueous humour from patients with acute corneal rejection. Acta Ophthalmol Scand 2005; 83:31-9. [PMID: 15715554]
- Duan X, Lu Q, Xue P, Zhang H, Dong Z, Yang F, Wang N. Proteomic analysis of aqueous humor from patients with myopia. Mol Vis 2008; 14:370-7. [PMID: 18334949]
- Richardson MR, Segu ZM, Price MO, Lai X, Witzmann FA, Mechref Y, Yoder MC, Price FW. Alterations in the aqueous humor proteome in patients with Fuchs endothelial corneal dystrophy. Mol Vis 2010; 16:2376-83. [PMID: 21139973]

- Bramsen T, Stenbjerg S. Fibrinolytic factors in aqueous humour and serum from patients with Fuchs' dystrophy and patients with cataract. Acta Ophthalmol (Copenh) 1979; 57:470-6.
   [PMID: 89778]
- Wilson SE, Bourne WM, Maguire LJ, Rahhal FM, Ribaudo RK, Kreutzer DL, O'Rourke J. Aqueous humor composition in Fuchs' dystrophy. Invest Ophthalmol Vis Sci 1989; 30:449-53. [PMID: 2784424]
- Bouhenni RA, Al Shahwan S, Morales J, Wakim BT, Chomyk AM, Alkuraya FS, Edward DP. Identification of differentially expressed proteins in the aqueous humor of primary congenital glaucoma. Exp Eye Res 2011; 92:67-75. [PMID: 21078314]
- Izzotti A, Longobardi M, Cartiglia C, Sacca SC. Proteome alterations in primary open angle glaucoma aqueous humor. J Proteome Res 2010; 9:4831-8. [PMID: 20666514]
- Grus FH, Joachim SC, Sandmann S, Thiel U, Bruns K, Lackner KJ, Pfeiffer N. Transthyretin and complex protein pattern in aqueous humor of patients with primary open-angle glaucoma. Mol Vis 2008; 14:1437-45. [PMID: 18682810]
- Duan X, Xue P, Wang N, Dong Z, Lu Q, Yang F. Proteomic analysis of aqueous humor from patients with primary open angle glaucoma. Mol Vis 2010; 16:2839-46. [PMID: 21203405]
- Fuchshofer R, Tamm ER. Modulation of extracellular matrix turnover in the trabecular meshwork. Exp Eye Res 2009; 88:683-8. [PMID: 19385040]
- Alvarado JA, Yeh RF, Franse-Carman L, Marcellino G, Brownstein MJ. Interactions between endothelia of the trabecular meshwork and of Schlemm's canal: a new insight into the regulation of aqueous outflow in the eye. Trans Am Ophthalmol Soc 2005; 103:148-62. [PMID: 17057799]
- Richardson MR, Price MO, Price FW, Pardo JC, Grandin JC, You J, Wang M, Yoder MC. Proteomic analysis of human aqueous humor using multidimensional protein identification technology. Mol Vis 2009; 15:2740-50. [PMID: 20019884]
- Keller A, Nesvizhskii AI, Kolker E, Aebersold R. Empirical statistical model to estimate the accuracy of peptide identifications made by MS/MS and database search. Anal Chem 2002; 74:5383-92. [PMID: 12403597]
- Nesvizhskii AI, Keller A, Kolker E, Aebersold R. A statistical model for identifying proteins by tandem mass spectrometry. Anal Chem 2003; 75:4646-58. [PMID: 14632076]
- Vesaluoma M, Mertaniemi P, Mannonen S, Lehto I, Uusitalo R, Sarna S, Tarkkanen A, Tervo T. Cellular and plasma fibronectin in the aqueous humour of primary open-angle glaucoma, exfoliative glaucoma and cataract patients. Eye (Lond) 1998; 12:886-90. [PMID: 10070530]
- Ogata N, Matsuoka M, Imaizumi M, Arichi M, Matsumura M. Decrease of pigment epithelium-derived factor in aqueous humor with increasing age. Am J Ophthalmol 2004; 137:935-6. [PMID: 15126162]
- Tezel G, Yang X, Luo C, Kain AD, Powell DW, Kuehn MH, Kaplan HJ. Oxidative stress and the regulation of complement activation in human glaucoma. Invest Ophthalmol Vis Sci 2010; 51:5071-82. [PMID: 20484586]
- O'Brien C, Butt Z, Ludlam C, Detkova P. Activation of the coagulation cascade in untreated primary open-angle glaucoma. Ophthalmology 1997; 104:725-9. [PMID: 9111270]

#### Molecular Vision 2011; 17:1891-1900 < http://www.molvis.org/molvis/v17/a206>

- Cullinane AB, Leung PS, Ortego J, Coca-Prados M, Harvey BJ. Renin-angiotensin system expression and secretory function in cultured human ciliary body non-pigmented epithelium. Br J Ophthalmol 2002; 86:676-83. [PMID: 12034692]
- Dan J, Belyea D, Gertner G, Leshem I, Lusky M, Miskin R. Plasminogen activator inhibitor-1 in the aqueous humor of patients with and without glaucoma. Arch Ophthalmol 2005; 123:220-4. [PMID: 15710819]
- Kinasewitz GT, Yan SB, Basson B, Comp P, Russell JA, Cariou A, Um SL, Utterback B, Laterre PF, Dhainaut JF. Universal changes in biomarkers of coagulation and inflammation occur in patients with severe sepsis, regardless of causative microorganism. Crit Care 2004; 8:R82-90. [PMID: 15025782]ISRCTN74215569
- 37. Wilson SE, Schultz GS, Chegini N, Weng J, He YG. Epidermal growth factor, transforming growth factor alpha, transforming growth factor beta, acidic fibroblast growth factor, basic fibroblast growth factor, and interleukin-1 proteins in the cornea. Exp Eye Res 1994; 59:63-71. [PMID: 7530663]
- Sekine-Okano M, Lucas R, Rungger D, De Kesel T, Grau GE, Leuenberger PM, Rungger-Brandle E. Expression and release of tumor necrosis factor-alpha by explants of mouse cornea. Invest Ophthalmol Vis Sci 1996; 37:1302-10. [PMID: 8641833]
- Heiser M, Hutter-Paier B, Jerkovic L, Pfragner R, Windisch M, Becker-Andre M, Dieplinger H. Vitamin E binding protein afamin protects neuronal cells in vitro. J Neural Transm Suppl 2002; (62):337-45. [PMID: 12456077]
- Chauhan V, Ji L, Chauhan A. Anti-amyloidogenic, anti-oxidant and anti-apoptotic role of gelsolin in Alzheimer's disease. Biogerontology 2008; 9:381-9. [PMID: 18704746]
- Paunio T, Kangas H, Kalkkinen N, Haltia M, Palo J, Peltonen L. Toward understanding the pathogenic mechanisms in gelsolin-related amyloidosis: in vitro expression reveals an abnormal gelsolin fragment. Hum Mol Genet 1994; 3:2223-9. [PMID: 7881424]
- Bucki R, Levental I, Kulakowska A, Janmey PA. Plasma gelsolin: function, prognostic value, and potential therapeutic use. Curr Protein Pept Sci 2008; 9:541-51. [PMID: 19075745]
- 43. Saccà SC, Pascotto A, Camicione P, Capris P, Izzotti A. Oxidative DNA damage in the human trabecular meshwork: clinical correlation in patients with primary open-angle glaucoma. Arch Ophthalmol 2005; 123:458-63. [PMID: 15824217]

- Tezel G. Oxidative stress in glaucomatous neurodegeneration: mechanisms and consequences. Prog Retin Eye Res 2006; 25:490-513. [PMID: 16962364]
- Ferreira SM, Lerner SF, Brunzini R, Evelson PA, Llesuy SF. Oxidative stress markers in aqueous humor of glaucoma patients. Am J Ophthalmol 2004; 137:62-9. [PMID: 14700645]
- 46. Zhang SX, Wang JJ, Gao G, Shao C, Mott R, Ma JX. Pigment epithelium-derived factor (PEDF) is an endogenous antiinflammatory factor. FASEB J 2006; 20:323-5. [PMID: 16368716]
- Zhou X, Li F, Kong L, Chodosh J, Cao W. Anti-inflammatory effect of pigment epithelium-derived factor in DBA/2J mice. Mol Vis 2009; 15:438-50. [PMID: 19247457]
- Takita H, Yoneya S, Gehlbach PL, Duh EJ, Wei LL, Mori K. Retinal neuroprotection against ischemic injury mediated by intraocular gene transfer of pigment epithelium-derived factor. Invest Ophthalmol Vis Sci 2003; 44:4497-504. [PMID: 14507898]
- Jung IL, Kang HJ, Kim KC, Kim IG. Knockdown of the Dickkopf3 gene induces apoptosis in a lung adenocarcinoma. Int J Mol Med 2010; 26:33-8. [PMID: 20514419]
- Nakamura RE, Hunter DD, Yi H, Brunken WJ, Hackam AS. Identification of two novel activities of the Wnt signaling regulator Dickkopf 3 and characterization of its expression in the mouse retina. BMC Cell Biol 2007; 8:52. [PMID: 18093317]
- Burger D, Dayer JM. High-density lipoprotein-associated apolipoprotein A-I: the missing link between infection and chronic inflammation? Autoimmun Rev 2002; 1:111-7. [PMID: 12849067]
- Opitz B, Eitel J, Meixenberger K, Suttorp N. Role of Toll-like receptors, NOD-like receptors and RIG-I-like receptors in endothelial cells and systemic infections. Thromb Haemost 2009; 102:1103-9. [PMID: 19967140]
- Erez E, Aravot D, Erman A, Sharoni E, Raanani E, Abramov D, Dijk DV, Sahar G, Vidne BA. Beta-2 microglobulin in heart transplanted patients. Transplant Proc 1997; 29:2706-7. [PMID: 9290798]
- Roxe DM, Siddiqui F, Santhanam S, del Greco F, Wolf J. Rationale and application of beta-2-microglobulin measurements to detect acute transplant rejection. Nephron 1981; 27:260-4. [PMID: 6167873]

Articles are provided courtesy of Emory University and the Zhongshan Ophthalmic Center, Sun Yat-sen University, P.R. China. The print version of this article was created on 11 July 2011. This reflects all typographical corrections and errata to the article through that date. Details of any changes may be found in the online version of the article.