C-reactive protein, procalcitonin, serum amyloid A) in a bedside-approach (detection from whole blood samples within 30 min). We demonstrate that the modulation of inflammatory mediators in septic plasma by means of selective adsorption significantly reduces endothelial activation in a cell culture model. We also discuss the role of extracellular microvesicles as markers and as potential targets for therapy.

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## Prognosticative biomarker clusters for polycystic kidney disease

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### Abstract

Polycystic kidney disease (PKD), in its autosomal recessive (AR) or autosomal dominant (AD) form, is characterized by the formation and expansion of numerous fluid-filled cysts within the kidneys. Quite often, the disease spreads to extrarenal territories including the liver. In addition to cyst formation, interstitial collagen deposition or scarring is sometimes observed in both kidney and liver. Progressive enlargement of the kidneys via replacement of the renal parenchyma with cysts and decreasing renal function makes ADPKD the leading genetic cause of renal transplantation. Highly aggressive fibrocystic kidney and liver disease in ARPKD means that many children with this form of disease do not live past the age of ten years. Using the PCK rat model of PKD, we have identify a minimally invasive biomarker cluster with high correlative value for fibrocystic disease progression. These results are important in that patient compliance, disease prognosis, interventional decisions and outcomes can be further and vastly improved by identification of minimally invasive or non-invasive biomarkers that are prognosticative of disease progression. Furthermore, rather than rely on a single biomarker, clinical outcomes may be better predicted by identification of a cluster of disease-relevant biomarkers which would bring increased correlation with disease progression. Clinical trials of therapeutics for chronic fibrotic diseases would also benefit from identification of such biomarkers given Big Pharma's reluctance to invest in trials wherein endpoints could be years away with no interim hint of success/failure. Identification of minimally invasive or non-invasive biomarkers in proliferative fibrocystic disease can better stratify children waitlisted for scarce kidneys and/or livers. The tangible outcome/technology/product that will result from the proposed research is biomarker-cluster chips designed to read urine or serum samples to determine disease progress or remission from disease. It is anticipated that these chips can eventually be mass produced in a relatively inefficient fashion and would have the predictive power ≥ imaging technologies but at far lesser cost and far lesser inconvenience. Eventually, this paradigm and the resulting technology may be extended to other diseases.

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## Proteomic profiling to identify markers of bacterial meningitis

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### Abstract

Bacterial meningitis is usually fatal without treatment and prompt and accurate diagnosis coupled with the timely administration of parenteral antibiotics are necessary in order to save lives. Despite the availability of highly effective antibiotics, the complications from bacterial meningitis (such as deafness, hydrocephalus, seizures and cerebral palsy) remain high. In areas with a high incidence of human immunodeficiency virus infection, Streptococcus pneumoniae is the commonest cause of bacterial meningitis. The diagnosis of bacterial meningitis can sometimes be delayed whilst samples are analysed in a laboratory using traditional methods of microscopy and antigen testing. We used cutting-edge high definition and quantitative mass spectrometry to identify specific protein signatures in cerebrospinal fluid associated with Streptococcus pneumoniae infection which could lead to the development of assays or point-of-care devices to improve the speed and accuracy of diagnosis, and consequently to enhance the prognosis of adults and children with bacterial meningitis. A range of samples (cases and controls, n = 12) from Malawian children has been analysed. Our data indicate some clear trends, and confirm that quantitative proteomics analysis will be successful in generating a comprehensive protein list from which markers might be nominated. We identified a total of 519 proteins in data dependent discovery proteomics and obtained quantitative data for 161 proteins using data independent Hi3 quantification. Using Progenesis LCMS we obtained a list of 202 potential candidates using data dependent acquisition approach and 109 using data independent acquisition, 82 proteins being common to both workflows. The protein profiles clearly differentiated cases and controls and have the potential to inform diagnosis and management of bacterial meningitis, especially in the developing world where the disease burden and mortality is greatest.

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## Claudin expression in animal models of IBD and human disease

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### Abstract

Claudins are transmembrane proteins constituting one of three tight junction protein families. There are 24 members of the claudin family identified, differently expressed in various cells/tissues and among species. In patients with inflammatory bowel disease (IBD), site and disease activity dependant changes in expression of certain claudins has been noted.

The aim of the study was to explore expression of claudins in the mouse models of IBD and to compare it to claudin expression in human disease.

The expression of several sealing claudins that are present in colon of humans and rodents has been evaluated by immunohistochemistry.

A decrease in claudin 1 expression was observed in a chronic mouse DSS model and adoptive transfer model of colitis, as it has been reported in human disease. Claudin 3 expression was not altered in the non-inflamed mucosa. Nevertheless, a subset of claudin 3 was internalized into cytoplasm of absorptive cells in inflamed mucosa in a chronic DSS model. In an adoptive transfer model of IBD, 8 weeks post-transfer, a reduction in claudin 3 expression was noted in surface colon epithelium as noticed in patients with Crohn's disease and ulcerative colitis. Claudin 8 expression decreased in the upper part of crypts, as is reported in patients with Crohn's disease. A subset of crypt base cells became strongly positive. Finally, a decrease in claudin expression in inflamed mucosa of human biopsies from patients with ulcerative colitis (UC) was observed.

In conclusion, it was shown that claudin 1, 3 and 8 expression pattern/intensity is altered in the mouse models of IBD in a same manner as observed in human biopsies from UC patients and described in patients with Crohn's disease.

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