Here, we took a systems biology approach to characterize phosphatases regulating mitosis. We performed a genome-wide RNAi screen targeting all human phosphatases.

We discovered several novel mitotic phosphatases, including CDKN3, and we have shown that CDKN3 inactivates cyclin-dependent kinases at the exit from mitosis by dephosphorylating Thr-161 of CDC2. We demonstrated that CDKN3 and CDC2 co-localize on centrosomes during mitosis and that loss of CDKN3 disrupts centrosome maintenance. We analyzed a phosphoproteome landscape of

CDKN3-deficient cells to reveal that CDKN3 knockdown leads to abnormal phosphorylation of multiple downstream cell cycle proteins, including CKβ. We have shown that CKβ phosphorylated at Ser-209 regulates the spindle checkpoint and localizes to centrosomes during mitosis. We confirmed that CDKN3 is required for mitosis in primary human brain stem cells, and we found that CDKN3 is lost in the glioblastoma multiforme brain tumors.

In summary, we have discovered a novel CDKN3/CDC2/CKβ tumor suppressor signaling axis. Our findings have diagnostic and therapeutic importance in cancer. Our discoveries enhance our comprehension of the cross-talk between mitotic phosphorylation cascades that maintain genomic stability. This signaling axis is a viable anti-cancer target in glioblastoma multiforme and other malignancies. Pre-clinical and clinical trials of small molecules targeting this signaling axis may lead to discoveries of novel anti-cancer chemotherapy strategies.

200 CIRCULATING PRO-ENDOTHELIN-1 (CT-PROET-1) AND PULMONARY MORBIDITY IN NEWBORN INFANTS

doi:10.1136/archdischild-2012-302724.0200

[1,2]S Wellmann, [2]J Benzing, [1]O Stabile, [2]G Szinnai, [3]NG Morgenthaler, [2]SM Schulzke, [3]C Bührer. *[1]University Hospital Zurich, Zurich; [2]University Children's Hospital Basel, Basel, Switzerland; [3]Charité University Medical Centre, Berlin, Germany*

Background and aims Plasma concentrations of endothelin-1 (ET-1), a potent pulmonary vasoconstrictor with a short serum half-life, can be estimated by measuring its stable by-product, C-terminal pro-Endothelin-1 (CT-proET-1). To investigate the association between CT-proET-1, gestational age, and pulmonary morbidity in newborn infants.

Methods A prospective cross-sectional study at two tertiary university hospitals was conducted. CT-proET-1 concentrations (pmol/L) were determined in plasma samples of 293 newborn infants (gestational age 24–41 weeks) at birth and on day 3 of life with BRAHMS KRYPTOR automated immunoflorescent assay.

Results At birth, CT-proET-1 concentrations were unrelated to birth weight and gestational age. Venous umbilical cord CT-proET-1 concentrations were consistently higher than matched arterial ones (M 148 vs. 134 pmol/L, p<0.001), but both values were closely related (R_S=0.745, p<0.001). There was large postnatal increase of CT-proET-1 in infants with pulmonary morbidity. Days of mechanical ventilation, continuous positive airway pressure (CPAP), and oxygen supplementation correlated each with CT-proET-1 level on day 3 (R_S 0.566, 0.658, and 0.819, respectively, for all p<0.001).

Conclusions In term and preterm newborn infants, pulmonary compromise is associated with increased concentrations of circulating CT-proET-1.

201 EFFICACY OF MONOTHERAPY WITH INHALED NITRIC OXIDE VERSUS COMBINATION WITH ORAL SILDENAFIL IN PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

doi:10.1136/archdischild-2012-302724.0201

SS Oguz, HG Kanmaz, E Dizdar Alyamac, FN Sari, O Erdeve, U Dilmen. *Zekai Tahir Burak Maternity Teaching Hospital Neonatology Unit, Ankara, Turkey*

Objective To evaluate the efficacy of combined therapy, sildenafil and inhaled nitric oxide versus monotherapy with inhaled nitric oxide in Pulmonary Hypertension of the Newborn.

Study Design A retrospective study.

Patients and Methods Newborn infants (gestational age greater than 34 weeks) who were presented with pulmonary hypertension from December 2008 to December 2010 were evaluated. Group I (n=14) received monotherapy with iNO and Group II (n=9) received combination therapy with iNO and oral sildenafil. Main outcome was to compare the duration of iNO therapy between groups.

Results Demographic characteristics were similar between the groups. As compared with the groups, combined therapy group had higher mean (SD) age of NICU admission (5.1±8.2 h vs. 21.3±36, h, p=0.01). Combination therapy was associated with early weaning of iNO (4.8±1.5 vs. 13.5±7.6 hours). The result showed that there is a reduced need for iNO therapy compared to monotherapy (75±44.6 vs. 112±95.2), however, the difference was insignificant (p=0.36). The incidence of mortality and outcomes were statistically insignificant between the groups (p>0.05).

Conclusions Combination therapy is significantly more effective in weaning of iNO and reduces the need for iNO therapy that is relatively expensive.

202 SURFACTANT AND INHALED NITRIC OXIDE FOR SEVERE RESPIRATORY DISTRESS COMPLICATED WITH PERSISTENT PULMONARY HYPERTENSION AMONG INFANTS BELOW 32 WEEKS GA

doi:10.1136/archdischild-2012-302724.0202

[1]A Adamczak, [2]S Gajos, [2]A Mejsak, [3]TA Merritt, [1]J Gadzinowski, [1]J Mazela. *[1]Neonatology; [2]Neonatal Research Club, Poznan University of Medical Sciences, Poznan, Poland; [3]Pediatrics, Loma Linda Medical Center, Loma Linda, CA, USA*

Introduction RDS can be complicated by PPHN due to intrauterine or postnatal prolonged hypoxia regardless of surfactant replacement therapy (SRT). Use of iNO therapy is not approved for premature infants < 34 weeks, nevertheless in most severe cases of PPHN use of iNO has been reported.

Aim The aim of this study was to analyze outcomes of infants with severe RDS treated with SRT and iNO in comparison to those treated with SRT only.

Methods Medical records from January 2008 till December 2010 from a level III NICU were analyzed. Only infants < 32 weeks ga and treated with SRT for RDS were included in the study divided in two groups: treated with SRT+iNO (PPHN based on SaO_2 differences and echocardiography) and SRT only. Data were analyzed according to maternal history: intrauterine infection, PROM, and clinical outcomes: pneumonia, NEC, ROP, BPD, IVH.

Results 309 premature infants < 32 weeks gestation were treated with SRT, with 54(17%) treated with iNO due to PPHN. There were significant higher ratios of intrauterine infection and early pneumonia in SRT+iNO in 2008 and 2009. The neonatal outcomes showed consistent higher incidence of ROP and PVL for the SRT+iNO group in these same years. The BPD rate remained unchanged at 20% and mortality ranged from 18 to 48%.

Conclusions Severe PPHN was likely caused by ineffective SRT due to presence of inflammation and possible surfactant inactivation. Inhaled NO improved oxygenation and decreased signs of PPHN but did not influence rate of BPD.

203 THE AVON LONGITUDINAL STUDY OF PAREANTS AND CHILDREN (ALSPAC) - WHAT DID WE LEARN?

doi:10.1136/archdischild-2012-302724.0203

A Ness. *University of Bristol, Bristol, UK*

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a transgenerational prospective observational study investigating influences on health and development across the life course. It has collected information on genetic, epigenetic, biological, psychological, social and other environmental exposures in relation to a diverse range of health, social and developmental outcomes. Recruitment sought to enrol pregnant women in the Bristol area of the UK during 1990–92. There were 13 761 women (contributing 13 867 pregnancies) recruited. This was extended to include additional children eligible using the original enrolment definition up to the age of 18 years. The children from 14 541 pregnancies were recruited in 1990–92, increasing to 15 247 pregnancies by the age of 18 years. The resource comprises a wide range of phenotypic and environmental measures in addition to biological samples, genetic and epigenetic information and linkage to health and administrative records. The study is celebrating its 21st Anniversary this year and over 700 peer-reviewed articles have been published using data from ALSPAC. The study has made contributions to understanding across a range of disciplines, exposures and outcomes. The presentation will present my view of the key contributions the study has made to date.

204 REGIONAL DIFFERENCES IN PERI- AND NEONATAL OUTCOMES OF EXTREMELY PRETERM INFANTS IN SWEDEN (EXPRESS)

doi:10.1136/archdischild-2012-302724.0204

[1]FH Serenius, [1]G Sjörs, [2]M Blennow, [3]V Fellman, [4]G Holmström, [5]K Marsal, [6]E Lindberg, [7]E Olhager, [8]L Stigson, [9]M Westgren, [10]K Källen, The EXPRESS Study Group. *[1]Women's and Children's Health, Uppsala University, Uppsala; [2]Dept of Pediatrics, Karolinska University Hospital, Huddinge, Stockholm; [3]Dept of Pediatrics, Lund University, Lund; [4]Dept Ophthalmology, Uppsala University, Uppsala; [5]Dept of Obstetrics and Gynecology, Lund University, Lund; [6]Dept of Pediatrics, Örebro University, Örebro; [7]Dept of Pediatrics, Linköping University, Linköping; [8]Dept of Pediatrics, Sahlgrenska University Hospital, Göteborg; [9]Dept of Obstetrics and Gynecology, Karolinska University Hospital, Huddinge, Stockholm; [10]Centre for Reproductive Epidemiology, Lund University, Lund, Sweden*

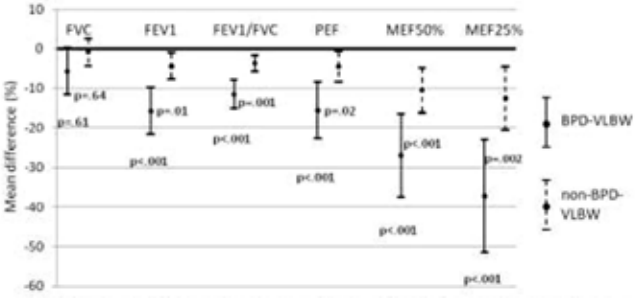
Background The EXPRESS study has shown favourable peri-and neonatal outcomes of extremely preterm infants (EPT, < 27weeks) in Sweden compared with similar studies.
Objective To determine whether there are differences in peri- and neonatal outcomes in spite of favourable national rates and whether outcomes can be related to regional differences in the use of perinatal interventions.
Methods Population-based prospective study of all EPT children born in Sweden from April1, 2004, to March 31, 2007. Of 1011 births, 707 were born alive and 497 survived to one year. Each region was assigned a perinatal activity score (PAS) based on the rate of selected perinatal interventions. Mortality rates were calculated, adjusted for background factors and related to PAS.
Results There were few regional differences in demographic background data. PAS varied from 74 to 100 (median 82) between regions. When 3 regions with the highest PAS (median 98) were compared with 4 regions with lower PAS (median 79), the following adjusted odds ratios (AOR) were found for infants born at 22–26 weeks: Perinatal death, AOR 0.6 (95%CL 0.4–0.8), infant mortality 0.6 (95% CI 0.4–0.9). There was no increase in the odds for survival with severe neonatal morbidity; AOR 0.7 (95% CI 0.5–1.0). When stratified by gestational age, increased survival was confined to infants born at 22–24 weeks. Regional differences were nullified when early deaths (< 12 hours) were excluded.
Conclusions There are differences in peri- and neonatal outcomes between regions in Sweden which can be explained by the intensity of perinatal interventions.

205 LUNG FUNCTION IN ADULTS BORN PRETERM - THE HELSINKI STUDY OF VERY LOW BIRTH WEIGHT ADULTS

doi:10.1136/archdischild-2012-302724.0205

[1]M Sipola-Leppänen, [1]HK Saarenpää, [1]M Tikanmäki, [2,3]P Hovi, [2,3]K Wehkalampi, [4]M Siltanen, [1,5]M Vääräsmäki, [2]AL Järvenpää, [3,6]JG Eriksson, [2]S Andersson, [2,3]E Kajantie. *[1]National Institute for Health and Welfare, Oulu; [2]Hospital for Children and Adolescents, Helsinki University Central Hospital; [3]National Institute for Health and Welfare, Helsinki; [4]Hyvinkää Hospital, Hyvinkää; [5]Department of Obstetrics and Gynaecology, Oulu University Hospital, Oulu; [6]Department of General Practice and Primary Health, University of Helsinki, Helsinki, Finland*

Backround and aims Adolescents born at very low birth weight (< 1500g, VLBW) have higher rates of respiratory symptoms and reduced lung function as compared with those born at term. Only few studies, however, have extended to adult life. We studied the association of preterm birth at VLBW with lung function in young adults.
Methods We used spirometry (Medikro®) to measure pulmonary function in 160 VLBW subjects and in 162 term-born controls (mean age 22.5 years) as a part of the Helsinki Study of Very Low Birth Weight Adults. BPD was diagnosed by a clinician based on Northway's criteria.
Results Figure 1 shows the mean values and differences in lung function tests between the groups. Forced expired volume in 1 second (FEV1), the FEV1/FVC (forced vital capacity) ratio, peak expiratory flow (PEF), maximal expiratory flow at 25% or 50% (MEF25% and 50%) were lower in adults born at VLBW than in those born at term. This finding was strongest in VLBW adults with a history of BPD but was present also in VLBW adults with no history of BPD.



Abstract 205 Figure 1 The mean difference in lung function test between VLBW adults with or without broncopulmonary dysplasia [BPD] (error bars) and term born controls (zeroline) adjusted for age, sex, height, BMI, parental education, maternal smoking during pregnancy, current daily smoking of the subject, and the frequency of leisure-time conditioning physical activity

The mean difference in lung function test.
Conclusions Reduced FEV1/FVC, PEF and $MEF_{25-50\%}$ suggest a medium and small airway obstruction among young adults born at VLBW. While this finding is strongest among BPD survivors, it is present also among VLBW adults with no history of BPD. This may be a risk factor for later obstructive pulmonary disease.

206 NEONATAL INFECTION AND 5-YEAR NEURODEVELOPMENTAL OUTCOMES OF VERY PRETERM INFANTS: THE EPIPAGE STUDY

doi:10.1136/archdischild-2012-302724.0206

[1,2]A Mitha, [3]PY Ancel, [1,2]P Truffert, [3]L Foix L'Hélias, EPIPAGE Study Group. *[1]NICU, Jeanne de Flandre Hospital; [2]Faculty of Medicine, Lille-Nord-de-France University, Lille; [3]Inserm Unit 953, Paris, France*

Background and aims To determine if neonatal infections are associated with increased risks of adverse neurodevelopment at 5 years of age in a population-based cohort of very preterm children.
Methods We included all live births between 22 and 32 weeks of gestation from 9 regions in France in 1997 (EPIPAGE study). Of the 2665 live-births, 2193 were eligible for follow-up evaluation at 5 years of age, 1769 had a medical examination and 1495 a cognitive