Agenda
from Eliot to Eliot

- Background
- Barker: developmental programming
- An endless story of trees
- Who are the actors of the scenario?
- Programming in the different organs
- U-shaped risk
- 3 examples: brain, heart, kidney
- 3 M and Maternal Milk: Metabolomics, Microbiomics, Multipotent stem cells
- Take-home messages
- Conclusions: 10 P Pediatrics
In my beginning is my end...

Thomas S. Eliot. Four Quartets
In my beginning is my end...
We had the experience but miss the meaning,
And approach to meaning restores the experience
In a different form, beyond any meaning...
The only wisdom we can hope to acquire is the wisdom of humility:
humility is endless.

Thomas S. Eliot. Four Quartets
What is life? (E. Schrödinger)

Le cinque grandi idee della biologia e della medicina (P. Nurse)

Cosa non buttare dalla mongolfiera

- Genoma
- Cellula
- Biochimica
- Evoluzione
- Biologia dei sistemi (systems biology)
Geographic Information System of a Human Being: one health, so many omics
The new languages of Medicine (I)
Metabolomics

- Systems Biology
- Systems Medicine
- Networks Medicine
- Omics Technologies
- Data trained Medicine
- Big data in Medicine
- Resilience, antifragility, fragility
- Olistic Medicine
- Individualized Medicine

Key word: complexity
The whole is not equivalent to the sum of its parts (Aristotle)
The new languages of Medicine (II)
Microbiomics

- Microbiota
- Olobionte
- Networking batterico
- Sociomicrobiologia batterica
- Ecosistema corporeo
- Co-evoluzione
- Simbiotici
- Sistema NEI (neuro-endocrino-immunitario)
- Batteri ed evoluzione del cervello
- Trapianto di microbiota
David Barker: the revolution that anticipates existence

Italo Farnetani¹, Vassilios Fanos²

¹Department of Surgery and Interdisciplinary Medicine, University of Milano – Bicocca, Milan, Italy
²Neonatal Intensive Care Unit, Puericulture Institute and Neonatal Section, AOU and University of Cagliari, Italy
Perinatal programming

“The response by a developing organism to a specific challenge during a critical time window that alters the trajectory of development qualitatively and/or quantitatively with resulting persistent effects on phenotype.”
Perinatal programming

“The response by a developing organism to a specific challenge during a critical time window that alters the trajectory of development qualitatively and/or quantitatively with resulting persistent effects on phenotype»
Perinatal programming

The response by a developing organism to a specific challenge during a critical time window that alters the trajectory of development qualitatively and/or quantitatively with resulting persistent effects on phenotype.

Are the fetus and the newborn father to the man?
During the Dutch Famine of 1944–1945, energy intake dropped from 1,800 to 400–800 calories per day for about 5 months.
... an endless story of trees
Struttura dell’albero bronchiale: un albero senza foglie, rovesciato, con i rami vuoti internamente.
“The total arborization of a neuron represents the graphic history of conflicts suffered during the developmental life”.

NO REGENERATION

Santiago Ramon y Cajal (1852 – 1934) Spanish pathologist, histologist, neuroscientist and Nobel laureate, the father of modern neuroscience
we have not yet unravelled the mystery of what is our brain.

looking to the patient, not to the disease.

PRECISION MEDICINE

Barack Obama, interview to Popular Science, 15 February, 2016

Ecole Polytechnique Fédérale de Lausanne, blue Brain Project 2008

Thirty millions connections between ten thousand neurons. The different colors indicate distinctive levels of electric activity.
Jackson Pollock, *Number 5*, 1948
The brain is not a computer, it is a jungle of trees
The kidney: How does it make a tree?

Metanephric mesenchyme and Branching ureteric bud
The Mysterious Tree of a Newborn’s Life
Understanding the Placenta, the least understood human organ
An innocent bystander?

By DENISE GRADY New York Times JULY 14, 2014

Placenta is the first of the trees of the organism: when it is strongly involved in pathologies, especially at ≤ 26 weeks of gestation, it probably determines a negative influence on all the other trees.

A print of a placenta was created by dipping the organ’s treelike branches in blue acrylic paint. The blood vessels that feed the branches were painted red before the blot was made.
What is a disease?

- Hypoplasia: less cells
- Dysplasia: less function

Reduction/inhibition of arborization
brain connections
bronchial tree
ureteric bud

.......... Reduction of vascular arborization
At high power (13,000X), interior of the liver mitochondria is presented, allowing a good evaluation of cristae volume and architecture. Mocci C, J Pediatr Neonat Individual Med. 2014
At high power (13,000X), interior of the liver mitochondria is presented, allowing a good evaluation of cristae volume and architecture. Mocci C, J Pediatr Neonat Individual Med. 2014
Fig. 2. Effect of prenatal low-protein diet on blood pressure in rats of various ages. Systolic blood pressure was measured by tail cuff in adult male (top) and female (bottom) rats whose mothers were fed a low-protein diet (6%) during the last half of pregnancy and compared with rats fed a normal protein diet (20%). There was a progressive increase of blood pressure with age in the low-protein group. Data are means ± SE; *P < 0.05; ***P < 0.001 [From Vehaskari et al. (137)].
Identical twins are not identical!

Same Genome/
Different Epigenome

• Acetylome
• Metylome
• Microbiome
• Virome
• Fungome
• Inflammasome
• Metabolome
• Phenome
• Diseasome
Who are the new actors of the scenario?
Minireview: Gut Microbiota: The Neglected Endocrine Organ

Gerard Clarke, Roman M. S.Ulling, Paul J. Kennedy, Catherine Stanton,
John R. Cryan, and Timothy G. Dinan

Alimentary Pharmabiotic Centre (G.C., R.M.S., P.J.K., C.S., J.F.C., T.G.D.) and Departments of Psychiatry
(G.C., C.S., T.G.D.) and Anatomy and Neuroscience (J.F.C.), University College Cork, Cork, Ireland; and
Teagasc (C.S.), Moorepark, Fennyside, Cork, Ireland

Germ-free animals are protected from high-fat diet-induced obesity

High-fat / High-sugar
Western diet

Obesity

Altered
Microbiota
Composition

Mol Endocrinol, August 2014, 28(8):1221–1238
Minireview: Gut Microbiota: The Neglected Endocrine Organ

Gerard Clarke, Roman M. Stilling, Paul J. Kennedy, Catherine Stanton, John F. Cryan, and Timothy G. Dinan

Alimentary Pharmabiotic Centre (G.C., R.M.S., P.J.K., C.S., J.F.C., T.G.D.) and Departments of Psychiatry (G.C., C.S., T.G.D.) and Anatomy and Neuroscience (J.F.C.), University College Cork, Cork, Ireland; and Teagasc (C.S.), Moorepark, Fermoy, Cork, Ireland

B

Germ-free animals adopt phenotype of microbiota donor

Donor weight
Microbiota Transfer
Adoption of phenotype
Normal
Obese
Underweight

Mol Endocrinol, August 2014, 28(8):1221–1238
Gut microbiota changes during pregnancy

Proteobacteria
Actionobacteria
Diversity
Fecalibacterion

Koren O.
Cell 2012
Dysbiosis of the gut microbiota in disease

Simon Carding\textsuperscript{1,2}, Kristin Verbeke\textsuperscript{3}, Daniel T. Vipond\textsuperscript{1,2}, Bernard M. Corfe\textsuperscript{4,5,}\textsuperscript{*} and Lauren J. Owen\textsuperscript{6}

\textsuperscript{1}Institute of Food Research, Norwich, UK; \textsuperscript{2}Norwich Medical School, University of East Anglia, Norwich, UK; \textsuperscript{3}Translational Research in GastroIntestinal Disorders, KU Leuven, Leuven, Belgium; \textsuperscript{4}Molecular Gastroenterology Research Group, Department of Oncology, University of Sheffield, Sheffield, UK; \textsuperscript{5}Insigneo

\begin{table}
\centering
\begin{tabular}{|l|l|l|}
\hline
Disease & Microbiota status & Disease impact \\
\hline
Inflammatory bowel disease & Germ free, antibiotics or probiotics & No disease or reduced severity \\
Spontaneous arthritis & Germ free & No disease \\
Autoimmune arthritis & Germ free & No disease \\
Autoimmune encephalomyelitis & Germ-free & Weak severity \\
Systemic lupus erythematosus & Germ free & No change \\
Type 1 diabetes & Germ free & No disease \\
Spontaneous ankylosing spondylitis & Germ free or probiotics & No disease \\
\hline
\end{tabular}
\caption{The intestinal microbiota and autoimmunity}
\end{table}
AVETE MAI VISTO DEI TOPI PRIVI DI GERMNI?

SONO ANIMALI SERIAMENTE INCASINATI!

MARIA GLORIA DOMINGUEZ-BELLO
Microbiologa presso la New York University
The microbiome in early life: implications for health outcomes

Maternal factors
- Vaginal infection
- Periodontitis

Postnatal factors
- Antibiotics
- Breast-feeding
- Host genetics
- Environment

Familial transmission
Environmental exposure

Microbiota changes
- Microbiota depletion
- Bifidobacterium
- Lactobacillus
- Christensenellaceae

Gut microbiota
- Lactobacillus
- Staphylococcus
- Propionibacterium

Birth
- Vaginal delivery
- Cesarean delivery

Infant (<1 year)
- Milk consumption
- Bifidobacterium
- Lactobacillus
- Vaillionella

Solid food introduction
- Bacteroides
- Clostridiales

Toddler (1–3 years)
- Full adult diet
- Adult-like microbiota
Lasting Impact of an Ephemeral Organ
The Role of the Placenta in Fetal Programming

Recent advances in ultrasonic and imaging technologies, 'omics', bioinformatics, and data sciences are offering researchers an unprecedented look at the placenta, the master regulator of the fetal environment.

© DMA/National Geographic Channel/Armby
The Placenta Harbors a Unique Microbiome
Kjersti Aagaard et al.
Sci Transl Med 6, 237ra65 (2014);
DOI: 10.1126/scitranslmed.3008599
Si stima che un lattante che ingerisce 800 ml di latte materno al giorno possa recepire, per questa via, fra i 100.000 e i 10.000.000 di batteri
The human neonatal gut microbiome: a brief review

Emily C. Girtz and Vineet Bhandari
Division of Perinatal Medicine, Department of Pediatrics, Yale Child Health Research Center, Yale University School of Medicine, New Haven, CT, USA

FIGURE 1 | Classification of common bacteria found in neonatal intestinal microbiome.
Antibiotics, birth mode, and diet shape microbiome maturation during early life

Maternal obesity during pregnancy and lactation programs the development of offspring non-alcoholic fatty liver disease in mice

Jude A. Oben1,2,*, Angelina Mourali-Murphy1,3, Anne-Maj Samuelsson3, Philippa J. Matthews3, Maelle L. Morgan3, Chad McKeel4, Junpei Soeda1, Denise S. Fernandez-Twinn4, Malgorzata S. Martin-Gronert1, Susan E. Ozanne4, Barbara Sigaia1, Marco Novelli4, Lucilla Poston1, Paul D. Taylor1

1University College London, Centre for Hepatology, Royal Free Hospital, London, UK; 2Guy’s and St. Thomas’ Hospital, Department of...
A microbial perspective of human developmental biology

Mark R. Charbonneau\textsuperscript{1,2}, Laura V. Blanton\textsuperscript{3,2}, Daniel B. DiGiulio\textsuperscript{3,4}, David A. Relman\textsuperscript{3,5}, Carlito B. Lebrilla\textsuperscript{6,7}, David A. Mills\textsuperscript{7,8,9} & Jeffrey I. Gordon\textsuperscript{1,2}

48 | NATURE | VOL 535 | 7 JULY 2016

Figure 1 | Oligosaccharides in human breast milk and strategies for their degradation by the infant microbiota. a, HMOs that are most abundant in the breast milk of mothers who are secretors are indicated by the blue arrow; those that are most abundant in the breast milk of non-secretors are indicated by the red arrow. Structures at the intersection of the arrows are found in both secretor and non-secretor mothers in similar abundances. Monosaccharides in HMOs, as well as their glycosidic linkages, are described by the inset key. b, Most strains of Bifidobacterium (left) use an ‘internalize, then degrade’ strategy in which HMO structures are first imported using ABC transporters and then degraded by intracellular glycoside hydrolases. Strains of Bacteroides (right) typically employ an ‘external degradation’ strategy for HMO structures, which involves cell-surface-associated carbohydrate-binding proteins and secreted glycoside hydrolases that are encoded by polysaccharide utilization loci (PULs). These PULs have features similar to the prototypical starch utilization system (Sus) of Bacteroides thetaiotaomicron. This external degradation can result in ‘cross-feeding’ of secondary consumers, including potentially pathogenic bacteria, in the infant gut microbiota.
Factors influencing the development of a personal tailored microbiota in the neonate, with particular emphasis on antibiotic therapy

G. Faa¹, C. Gerosa¹, D. Fanni¹, S. Nemolato¹, P. van Eyken³, and V. Fanos²

¹Department of Surgical Sciences, Division of Pathology, University Hospital San Giovanni di Dio, University of Cagliari, Cagliari, Italy
²NIC, Paediatrics Institute and Neonatal Section, University Hospital San Giovanni di Dio, University of Cagliari, Cagliari, Italy, and ³Department of Pathology, K.U. Leuven, Leuven, Belgium

Obesity?
Autism?
The urinary metabolomics profile of an Italian autistic children population and their unaffected siblings

Antonio Noto, Vasillis Fanos, Luigi Barberini, Dmitry Grapov, Claudia Fattuoni, Marco Zaffanello, Andrea Casanova, Gianni Fenu, Andrea De Giacomo, Maria De Angelis, Corrado Moretti, Paola Papoff, Raffaella Ditonno, and Ruggiero Francavilla
Abnormal metabolites arising from anaerobic bacteria of the gut (Clostridia spp.). Elevated in urine in previous studies on autism. Decrease after treatment with oral vancomycin: a valid biomarker for Clostridia spp.
Do each of these babies have different adult health fates?
Urinary metabolomics (GC-MS) reveals that low and high birth weight infants share elevated inositol concentrations at birth

Luigi Barberini¹, Antonio Noto², Claudia Fattuoni³, Dmitry Grapov⁴, Andrea Casanova⁵, Gianni Fenu⁶, Mauro Gaviano⁶, Roberta Carboni², Giovanni Ottonello³, Maurizio Crisafulli³, Vassilios Fanos⁶, and Angelica Dessi²

AUC = 1
Physiopathology of intrauterine growth retardation: from classic data to metabolomics

Angelica Dassi1, Giovanni Ottolino2 & Vassilios Fanos1

1 Neonatal Intensive Care Unit, Paediatric Intensive Care Unit and Neonatal Section, AOU Cagliari, Italy; 2 Department of Surgery, Section of Neonatal Intensive Care Unit and PICU, University of Cagliari, Cagliari, Italy

Figure 1. Metabolic state characterizing SGAs and LGAs from foetal life to birth.

Molecules 2013, 18, 11725-11732; doi:10.3390/molecules181011724

Molecules and Fetal-Neonatal Nutrition: Between “Not Enough” and “Too Much”

Angelica Dassi, Melania Puddu, Giovanni Ottolino and Vassilios Fanos

Neonatal Intensive Care Unit, Paediatric Intensive Care Unit and Neonatal Section, Azienda Ospedaliera Universitaria, Cagliari 09124, Italy

Review Article

Clinical Metabolomics and Nutrition: The New Frontier in Neonatology and Pediatrics

Angelica Dassi, Flaminia Cesare Marincola, Alice Masili, Diego Gazzolo, and Vassilios Fanos
RISCHIO CARDIOVASCOLARE

INSUFFICIENZA RENALE CRONICA

DIABETE

AUTISMO
The placenta is the center of the chronic disease universe

Kent L. Thornburg, PhD; Nicole Marshall, MD

October 2015

The figure shows the risk of coronary heart disease based on the ratio of placental weight to birthweight in an English population. Low placental weight to birthweight is defined as efficient and represented by the left-hand bars. This U-shaped curve suggests that placental efficiencies are related to the risk for disease. This relationship has been found in other studies as well.
Segmento 2.
Sviluppo del cervello: come si forma una giungla
A baby’s brain at 35 weeks weighs only two-thirds of what it will weigh at 40 weeks.
A baby’s brain at 35 weeks weighs only two-thirds of what it will weigh at 40 weeks.
Fetal Programming of the Human Brain: is there a Link with Insurgence of Neurodegenerative Disorders in Adulthood?

Author(s): G Faa, M A. Marcialis, A Ravarino, M Piras, M C Pintus and V Fanos
Aluminum exposure and toxicity in neonates: a practical guide to halt aluminum overload in the prenatal and perinatal periods

Daniela Fanni, Rossano Ambu, Clara Gerosa, Sonia Nemolato, Nicoletta Iacovidou, Peter Van Eyken, Vassilios Fanos, Marco Zaffanella, Gavino Faa
Cagliari, Italy

Background: During the last years, human newborns have been overexposed to biologically reactive aluminum, with possible relevant consequences on their future health and on their susceptibility to a variety of diseases. Children, newborns and particularly preterm neonates are at an increased risk of aluminum toxicity because of their relative immaturity.

Based formulas in which, on the basis of recent studies, there is still too much aluminum.

World J Pediatr 2014;10(2):??-??

Key words: aluminum; newborn;

<table>
<thead>
<tr>
<th>Sources</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast milk</td>
<td>10 mg</td>
</tr>
<tr>
<td>Infant formula</td>
<td>40 mg</td>
</tr>
<tr>
<td>Soy-based formula</td>
<td>120 mg</td>
</tr>
<tr>
<td>Vaccines</td>
<td>4 mg</td>
</tr>
<tr>
<td>Parenteral nutrition</td>
<td>grams</td>
</tr>
<tr>
<td>Antiacids</td>
<td>unknown</td>
</tr>
</tbody>
</table>

Aluminum sources that infants may receive during the first 6 months of life
I consigli per le mamme in gravidanza!

- Evitare di bere bevande acide (specie gassate) o the in contenitori di alluminio.
- Restringere l’assunzione di the e preferire l’aggiunta di latte (riduce la biodisponibilità) a quella del limone (aumenta assorbimento)
- Limitare l’uso di dentifrici e traspiranti contenenti alluminio.
- Evitare l’assunzione di caffè ottenuto con la moka in alluminio.
- Limitare il consumo di cibi cotti o conservati in contenitori di alluminio.
- Evitare formaggi o dolci contenenti alluminio.
- Evitare l’assunzione di erbe ove non sia specificato il livello di contaminazione da alluminio.

- Evitare, durante l’allattamento, l’uso di prodotti di bellezza contenenti alluminio.
- Scegliere le formule laitée con minore contenuto di alluminio.
- Scegliere le acque minerali con minore contenuto di alluminio per diluire le formule lattee.
- Porre grande attenzione alle formule di soia per l’elevato contenuto di alluminio.
- Porre grande attenzione alle terapie parenterali per l’elevato contenuto di alluminio.
- Evitare i farmaci contenenti alluminio, in particolare gli antiacidi.
- Non rimandare la vaccinazione con vaccini contenenti alluminio (la quantità è modesta.

FANNI D, FANOS V, ...FAA G. WORLD J PEDIATRICS 2014
Ethanol exposure during pregnancy causes apoptosis of Purkinje cells and cerebellar granule cells.

Messaggio da portare a casa: alcol zero!!!

Luo J, Cerebellum 2012, 31, 543-549
SMOKE

SPONTANEOUS ABORTION
PREMATURITY
PREMATURE RUPTURE OF MEMBRANES

SMALLER FRONTAL LOBES
- IMPAIRED EMOTION CONTROL

DECREASED CEREBELLAR VOLUME
DECREASED ATTENTION ABILITY
IMPAIRED IMPULSE CONTROL
BEHAVIORAL DYSORDERS

CHANGES IN:
- NORADRENERGIC SYSTEM
- SEROTONINERGIC SYSTEM
- DOPAMINERGIC SYSTEM

MOTOR DEFICITS

PREFRONTAL CORTEX DEVELOPMENT
COGNITIVE DYSORDERS

HIPPOCAMPAL DISFUNCTION
MEMORY DEFICIENCY

Fanos V et al. BMC Embryo Today, submitted
Perinatal Heart Programming: Long-term Consequences

A. Faa¹, R. Ambu¹, G. Faa¹ and V. Fanos²

¹Department of Surgical Sciences, Section of Pathology, University of Cagliari, Cagliari, Italy; ²NICU, Paediatric Intensive Care Institute and Neonatal Section, University of Cagliari, Cagliari, Italy

Prematurity and low weight at birth as new conditions predisposing to an increased cardiovascular risk

Giuseppe Mercuro¹, Pier Paolo Bassareo¹, Giovanna Flore¹, Vassilios Fanos¹, Ilaria Dentamaro², Pietro Sciacchitano², Nicola Lafor gia² and Marco Matteo Ciccone²
# The Cagliari Experience

## Table 1. Characteristics of the population in the study

<table>
<thead>
<tr>
<th></th>
<th>ex-ELBW ($n = 30$)</th>
<th>Control group ($n = 30$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>$20.3 \pm 2.4$</td>
<td>$20.8 \pm 1.6$</td>
<td>0.9</td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>0.5</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>$832.4 \pm 116.5$</td>
<td>$3,138.1 \pm 759.7$</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>$27.7 \pm 2.1$</td>
<td>$39.3 \pm 1.5$</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>$161.3 \pm 4.2$</td>
<td>$167.5 \pm 2.9$</td>
<td>0.08</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>$51.8 \pm 4.7$</td>
<td>$56.4 \pm 3.2$</td>
<td>0.07</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>$19.7 \pm 1.4$</td>
<td>$20.4 \pm 0.9$</td>
<td>0.7</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>$132 \pm 5$</td>
<td>$124 \pm 6$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>IVS (mm)</td>
<td>$9.9 \pm 0.5$</td>
<td>$8.7 \pm 0.6$</td>
<td>$&lt;0.01$</td>
</tr>
<tr>
<td>PW (mm)</td>
<td>$8.4 \pm 0.5$</td>
<td>$7.7 \pm 0.4$</td>
<td>$&lt;0.01$</td>
</tr>
<tr>
<td>LV mass (g/m²)</td>
<td>$119.1 \pm 4.3$</td>
<td>$111 \pm 4.9$</td>
<td>$&lt;0.01$</td>
</tr>
</tbody>
</table>

ex-ELBW, ex-extremely low birth weight; BMI, body mass index; IVS, interventricular septum; PW, posterior wall; LV, left ventricular.
### Long term problems in young adults born ELBW


<table>
<thead>
<tr>
<th>Observed results</th>
<th>Practical consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolongation in QT interval</td>
<td>Risk of sudden death</td>
</tr>
<tr>
<td></td>
<td>Monitor ECG</td>
</tr>
<tr>
<td></td>
<td>Avoid drugs prolonging QT</td>
</tr>
<tr>
<td>Reduced brachial-flow mediated vasodilatation</td>
<td>Risk of hypertension</td>
</tr>
<tr>
<td></td>
<td>Monitor blood pressure</td>
</tr>
<tr>
<td>High levels of asymmetric dimethylarginine (ADMA), a strong inhibitor of nitric oxide synthesis</td>
<td>Risk of future cardiovascular events and cardiac death</td>
</tr>
<tr>
<td></td>
<td>Monitor blood pressure, echocardiography</td>
</tr>
<tr>
<td>Dramatic Increase of microalbuminuria, uNGAL (Neutrophil Gelatinase Associated Lipocalin) Decrease of renal volume</td>
<td>Risk of chronic renal failure</td>
</tr>
<tr>
<td></td>
<td>Monitor creatininemia, cystatin C, microalbuminuria, urine dipstick</td>
</tr>
</tbody>
</table>
Significant QT interval prolongation and long QT in young adult ex preterm newborns with extremely low birth weight

Pier Paolo Bassareo¹, Vassilios Fanos², Melania Puddu², Christian Cadeddu¹, Marta Balzarini¹, Giuseppe Mercuro (JMFNM 2010)
Epicardial fat thickness, an emerging cardiometabolic risk factor, is increased in young adults born preterm

P. P. Bassareo\textsuperscript{1*}, V. Fanos\textsuperscript{2}, M. Puddu\textsuperscript{2}, S. Marras\textsuperscript{1} and G. Mercuro\textsuperscript{1}

\textsuperscript{1}Department of Medical Sciences ‘M. Arsu’, University of Cagliari, Cagliari, Italy
\textsuperscript{2}Department of Pediatrics and Clinical Medicine, Section of Neonatal Intensive Care Unit, University of Cagliari, Cagliari, Italy

Fig. 2. Comparison of epicardial fat thickness (EFT) between the two groups [ex-extremely low birth weight (ex-ELBW) v. controls: 8.7 ± 0.7 v. 5.6 ± 0.9 mm].
Differences in the two groups related to the alterations in the arginine and proline metabolism, in the purine and pyrimidine metabolism in the hystidine, beta-alanine metabolism and with the urea cycle
(Fanos V. et al Clinical Biochemistry 2011, mod)
DEVELOPMENTAL NEPHROLOGY:
FROM EMBRYOLOGY TO METABOLOMICS

V. Fanos
R. L. Chevalier
G. Faa
L. Cataldi

Kidney Development in Renal Pathology

Gavino Faa
Vassilios Fanos Editors

Humana Press
Barker hypothesis
Altered embryonic/fetal development results in low birthweight and predisposes for adult diseases (renal, metabolic, cardiovascular)

Brenner hypothesis
Low nephrons number predisposes to adult hypertension

Events
Prenatal perturbation

Main Modifiers
Perinatal Programming

Extreme prematurity
Low birth weight
Nutritional setting
Catch-up growth
Obstructive and refluxing nephropathy
Nephrotoxic drugs
What Perinatologist do not know ...

• Preterm infant: window of 6 wks of postnatal renal maturation
  ex. 24 wks: maturation until 30 wks → stop

• Preterm infant with acute kidney failure: window of 4 wks of postnatal renal maturation
  ex. 24 wks: maturation until 28 wks → stop

• If IUGR: maturation window further reduced

Reduction final number of nephrons
Variability in total nephron number for single kidney at birth

CLINICAL SIGNIFICANCE (basal value + postnatal kidney injury)

200,000

900,000

2,500,000

IUGR

NSAIDs

NEPHROTOXIC FACTORS (NUTRITIONAL RESTRICTION & DRUGS)
Immunoistochimica tissutale

Marcatori in corso di studio
Collaborazione Prof. G. Faa

- WT1
- MUC1
- CD10
- CD44
- Proteina mTOR
- BCL2
- BCL1
- Kim1
- Timosina beta 4
- Timosina beta 10
- hCTR1
- Glypican 3
- Galectina
- ……
Role of immunohistochemistry: to give a name to actors of nephrogenesis
Neonatal Physiological Rigenerative Medicine?

IUGR
LOW CALORIC INTAKE
OR "TOO FAVOURABLE
DRUGS (NSAIDS, AMG)
HYPEROXIA
HYPOXIA

WEIGHT AGA
ADEQUATE CALORIC
INTAKE
DRUGS (VIT. A)
NORMOXIA

800.000

400.000

1.600.000

NUMBER OF NEPHRONS

APOPTOSIS

MITOSIS

* matching genetic/epigenetic requirement

The kidney of late preterm infants
Vassilios Fanos1,2, Clara Gerosa1,2, Davide Fanni1,3, Cristina Ludda2,3, Stefano Toppo2, Giovanni Ottenino1,4, Davide Fazi5
From XXIX National Congress of the Italian Society of Neonatology
https://www.jponline.net/content/40/02/A14

“Physiological” renal regenerating medicine in VLBW preterm infants: could a dream come true?
Daniela Fanni1, Clara Gerosa1, Sonia Nemolato1, Cristina Mocci1, Giuseppina Pichiri1, Pierpaolo Costi1, Terezie Conglu2, Marco Pilus3, Monica Pirisi4, Matteo Fraschini5, Marco Zafantell6, Nicoletta Ioaviddou5, Peter Van Eylen7, Guido Moniga5, Davide Fazi5 & Vassilios Fanos5
Metabolomics, milk-oriented microbiota (MOM) and multipotent stem cells: the future of research on breast milk

Vassilios Fanos

Neonatal Intensive Care Unit, Neonatal Pathology, Puericulture Institute and Neonatal Section, “Azienda Ospedaliero Universitaria” and University of Cagliari, Cagliari, Italy

Mamma sarda che allatta in costume tipico
A metabolomic study of preterm human and formula milk by high resolution NMR and GC/MS analysis: preliminary results

Flaminia Cesare Marincola1,6, Antonio Noto2,6, Pierluigi Caboni3, Alessandra Reali2, Luigi Barberini4, Milena Lussu5, Federica Murgia5, Maria Laura Santoru5, Luigi Atzori6 & Vassilios Fanos2

Figure 1. $^1$H NMR spectra of a formula milk (FM) (a) typical preterm human breast milk (HBM) (b) aqueous extract in $D_2O$. 
NMR (aqueous phase): Principal Component Analysis (PCA)
Tallin 2012, Proceedings 20th European Workshop on Neonatology,

Using the best formula for the patient, when mother’s milk is not available

Human Milk
Formula Milk

Maltose, Myo-inositol, Lactose, Glucose, Galactose
Alanine, Valine, Leucine, Isoleucine, Glutamate
Citric, Lactic, Fumaric acid, Creatine, Phospho/creatine, Creatinine, Taurine

Milk of mothers who delivered a preterm baby
Clinical Impact of Human Breast Milk Metabolomics

<table>
<thead>
<tr>
<th>Aim of study</th>
<th>Population studied</th>
<th>Samples type</th>
<th>Platform</th>
<th>Most variable metabolites</th>
<th>Direction of magnitude variations</th>
<th>First author (year) Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison between the metabolic profiles of preterm HBM and formula milk (FM)</td>
<td>Mothers delivering preterm infants (n=20)</td>
<td>Hydrosoluble and liposoluble extracts</td>
<td>H-NMR GC-MS</td>
<td>Lactose, Maltose, Oleic, linoleic</td>
<td>↑ HMB↑</td>
<td>Cesare Marincola F (2012) [12]</td>
</tr>
<tr>
<td></td>
<td>* Mothers giving birth full-term infants (n=1)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>* Formula milks commonly used for preterm infants (n=13)</td>
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</tr>
<tr>
<td>Influence of maternal phenotype on HBM composition in HBM</td>
<td>Mothers delivering term infants (n=29)</td>
<td>Hydrosoluble extract</td>
<td>'H-NMR</td>
<td>' 3-FL, LNDFH II and derivatives</td>
<td>↑ Le-positive non-Secretory↑</td>
<td>Praticò G (2014) [23]</td>
</tr>
<tr>
<td>Influence of maternal phenotype and diet on the HBM metabolism</td>
<td>Mothers delivering term infants (n=52)</td>
<td>Hydrosoluble extract</td>
<td>'H-NMR</td>
<td>' 2′-FL, LDFT, LNFF I, fructose</td>
<td>↑ Secretory↑</td>
<td>Shalowitz JT (2014) [24]</td>
</tr>
<tr>
<td>Development of a single-phase extraction method suitable for both GC-MS and LC-MS to characterize HBM over the first four months and characterization of differences in HBM composition within the first month post-partum</td>
<td>Mothers delivering term infants (n=52)</td>
<td>Organic extract</td>
<td>LC-MS GC-MS</td>
<td>Linoleic acid, Palmitoleic acid, Oleic acid, LPE, Gliconic acid, Hydroxyacids, acids, NDO, TO</td>
<td>↑ at more than 26 days post-partum↑</td>
<td>Villasenifi A (2014) [18]</td>
</tr>
<tr>
<td>Comparison between the metabolic profile of HBM and formula milk (FM)</td>
<td>* Mothers delivering between 27 and 41 weeks of gestation (n=20)</td>
<td>Hydrosoluble extract</td>
<td>'H-NMR</td>
<td>Lactose, Galactose 1-phosphate and Maltose</td>
<td>↑ HMB↑</td>
<td>Longini M (2014) [17]</td>
</tr>
<tr>
<td></td>
<td>* Formula milks recommended for newborn with different birthweight (n=4)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Human breast milk stem cells: a new challenge for perinatologist

Giuseppina Pichirri¹, Daniele Lanzano¹, Monica Piras¹, Angelica Dessi², Alessandra Reali³, Melania Puddu³, Vassilios Fanos², Gavino Faa¹, Pierpaolo Coni¹

¹Department of Surgical Sciences, Section of Pathology, University of Cagliari, Cagliari, Italy
²Neonatal Intensive Care Unit, Neonatal Pathology, Paediatric Institute and Neonatal Section, AOUE and University of Cagliari, Cagliari, Italy

CD 44 good marker of stemness

CD 133 positive only in the first 3 days

Ki67 marker of asymmetric division

Could metabolomics be useful for studying stem cells in breast milk? Correlation with presence and percentage of stem cells
BREASTMILK STEM CELL TRANSFER FROM MOTHER TO NEONATAL ORGANS

Maternal stem cells may:
- Migrate across the intestinal Barrier
- Differentiate
- Assimilate and integrate with newborn tissues

Hassiotou F. Faseb Journal 2014, 28
Programmazione della salute e della malattia da parte del latte materno

Le cellule staminali del latte materno

Prof G. Faa Cagliari

Twigger A-J J Hum Lact, 2013
FROM BREAST MILK TO BRAIN

Differentiation of breast-milk stem cells to neural stem cells and neurons.

- Neurons
- Oligodendrocytes
- Astrocytes
- Metabolomica liquido cellule staminali

Hosseini SM Neurol Res Int 2014
In collaborazione con l’Università di Atene:
Prof.ssa Malamitsi-Puchner
(dati non pubblicati)

Cellule CD44 +

IUGR = 20 volte maggiori
Radici Profonde...
Messaggi da portare a casa

• Periodi critici di vulnerabilità → (“trasformare le finestre di vulnerabilità in finestre di opportunità”).
• Il *programming* determina cambiamenti strutturali permanenti in organi importanti (*God save the brain...*) e può modificare la suscettibilità alle malattie.
• La placenta svolge un ruolo chiave (“E’ la placenta un *innocent bystander*, un testimone innocente? No, non lo è”).
• Il compenso che si verifica vuole farci raggiungere l’immortalità (“*Per riprodurmi, son nato*”) ma ha dei costi (“una tassa da pagare”).
• Gli effetti del *programming* sono transgenerazionali. Dallo slogan paradossale “devi sceglierti i genitori” al “devi sceglierti i genitori, i nonni e i bisnonni!”

*Fanos V. Metabolomica e microbiomica. Hygeia Press 2015*
Siamo tutti diversi

Straordinaria variabilità interindividuale basale che aumenta dopo uno stimolo intenso (es. asfissia, sepsi, digiuno prolungato....)

Concetti di FRAGILITA’ E RESILIENZA
EARLY INTERVENTIONS COULD PREVENT EARLY ONSET

PRENATAL
• Prudent diet
• Micronutrients
• Avoid toxic substances

POSTNATAL
• Close monitoring
• Appropriate lifestyle
  - promote physical activity,
  - avoid secondary smoking,
  - prevent obesity
• Dietary interventions
  - breastfeeding
  - avoid rapid growth periods
  - monitor newborns at risk

What to do?
I have a dream

PEDEIATRICS of 10 P

- Personalized
- Prospective
- Predictive
- Preventive
- Precise
- Participated
- Patient-centered
- Psycocognitive
- Postgenomic
- Public
12th International Workshop on Neonatology
October 19th–22nd, 2016
T'Hotel, Cagliari, Italy

10 P Pediatrics: notes for the future

With 8 satellite meetings

Main topics
Cardiology • Developmental Origin of Health and Disease • Infectiology • Laboratory Medicine • Metabolomics • Nephrology • Nutrition • Obstetrics • Pathology • Perinatology • Pediatrics in High-Risk Areas • Pharmacology

JPNIM’s presentation

Abstracts
Abstracts will be published in the Journal of Pediatric and Neonatal Individualized Medicine (JPNIM)
Deadline: August 15th, 2016
5 awards (500 euros each)

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E-mail: monica.arosio@biomedia.net
In my beginning is my end...

Four Quartets
In my beginning is my end...

Four Quartets

...Pray for us now and at the hour of our birth.

Animula
Grazie
dell’attenzione
Are we born with innate knowledge, ideas and virtues?

**YES**

PLATO

THE PERFORMATION THEORY

GENETIC VIEW

**NO**

ARISTOTE

THE BLANK SLATE

EPIGENETIC VIEW
Are we born with innate knowledge, ideas and virtues?

YES
PLATO
THE PERFORMATION THEORY

NO
ARISTOTLE
THE BLANK SLATE

GENETIC VIEW
EPIGENETIC VIEW

2/3
Acknowledgments and permanent collaborations

Luigi Atzori, Luigi Barberini
Scienze Neur. e Cardiovascolari,
University of Cagliari

Melania Puddu, Giovanni Ottonello,
Antonio Noto, Angelica Dessì
NICU Cagliari

Emanuela Locci, Flaminia Marincola,
Paola Scano Dip. Scienze Chimiche,
University of Cagliari

Michele Mussap
San Martino Hospital, Univ. of Genoa

Dmitry Grapov, California, USA

Giuseppe Buonocore, Univ. of Siena

Julian Griffin
Department of Biochemistry
University of Cambridge

Aalim Weljie
Metabolomics Research Centre
Univ. of Calgary

95 collaborations with 19 countries in 5 continents
Both undernutrition and overnutrition are MALNUTRITION.
4 DECEMBER 2015

ITALIAN SOCIETY
DOHaD

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SERGIO BERNASCONI
GIAN CARLO DI RENZO
LUCA RAMENGHI
VASSILIOS FANOS
BENITO CAPPuccini
LUCIA MIGLIore
ERNESTO BURGIO
GIAN PAOLO DONZELLI
FEDERICO MECACCI
4 DICEMBRE 2015

GRUPPO COSTITUENTE
DOHAD SOCIETY ITALY

VASSILIOS FANOS
(RESPONSABILE) vafanos@tin.it

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VASSILIOS FANOS
BENITO CAPPUCCINI
LUCIA MIGLIORE
ERNESTO BURGIO
GIAN PAOLO DONZELLI
FEDERICO MECACCI
The Human Kidney at Birth: Structure and Function in Transition

Robert L. Chevalier and Jennifer R. Charlton

Structure does not determine Function or vice versa, but both are simply different ways of regarding and describing the same thing.

—Jean R. Oliver, *Nephrons and Kidneys* 1968
In my beginning is my end...
We had the experience but miss the meaning,
And approach to meaning restores the experience
In a different form, beyond any meaning...
The only wisdom we can hope to acquire
Is the wisdom of humility:
humility is endless.

Thomas S. Eliot. *Four Quartets*
Group 1 (spontaneous) related to group 3 (cesarean) at birth.

Higher

0.62 (s) ppm
1.24 (sb) ppm suberic acid
1.27 (sb) ppm sebacic acid
1.63 (s) ppm alpha-amino adipic acid (to confirm)
2.72 (s) ppm dimethylamine
3.208 (s) Choline
3.02, 1.73(m), Lysine
4.08 (m) Myoinositol
7.84 Hippurate
7.09, 7.91 (s) Histidine
2.06 (sb) ppm Glycoprotein signal
2.08 (sb) ppm Glyco protein signal
2.38 (s) oxaloacetate
2.43 (s) beta-keto-adipic acid
Geographic Information System of a Human Being
The new languages of Medicine

- Microbiota
- Olobionte
- Networking batterico
- Sociomicrobiologia batterica
- Ecosistema corporeo
- Co-evoluzione
- Simbiotici
- Sistema NEI (neuro-endocrino-immunitario)
- Batteri ed evoluzione del cervello
- Trapianto di microbiota
Leonardo da Vinci studies of the fetus on the womb: circa 1510-1513
8th International Workshop on Neonatology, Cagliari 24-27 October 2012
Differences in the two groups related to the alterations in the arginine and proline metabolism, in the purine and pyrimidine metabolism in the hystidine, beta-alanine metabolism and with the urea cycle (Fanos V. et al. Clinical Biochemistry 2011, mod)

Metabolomics in adult patients (mean age 24 years) born at Term

born ELBW

24 years
Urinary Metabolomics and Systemic Scleroderma: Preliminary Investigation on Early Diagnosis and Classification Potential.

Francesco Palmas, Antonio Noto, Claudia Fattuoni, Carolina Amador, Angelica Dessi, Luigi Barberini, Vassilios Fanos, Gianpaolo Donzelli.
Original Article

Urinary metabolomics of bronchopulmonary dysplasia (BPD): preliminary data at birth suggest it is congenital

Vassilios Fanos¹, Maria Cristina Pintus², Milena Lussu³, Luigi Atzori³, Antonio Noto¹, Mauro Stroam², Hercilia Guimaraes⁴, Gustavo Rocha⁴, Corrado Metetti¹, Paola Papoff⁴, Serafina Lacerenza², Silvia Puddu¹, Francesca Serraino², Michele Mussap³, and Giovanni Corsello¹
Who do we think we are?

- Cellule organismo
- Microbiota
- Viroma
- Fungoma
- Chimerismo
Diverse mammals, including humans, have been found to carry distinct genomes in their cells. What does such genetic chimerism mean for health and disease?

By Elena E. Giorgi | April 1, 2015
Fetal microchimerism and maternal health: A review and evolutionary analysis of cooperation and conflict beyond the womb

Amy M. Boddy, Angelo Fortunato, Melissa Wilson Sayres and Athena Aktipis

Mother-Offspring Tug-of-War

<table>
<thead>
<tr>
<th>Offspring's Interest</th>
<th>Mother's Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upregulation of neuroendocrine systems underlying parental investment and bonding</td>
<td>Modulation of systems underlying parental investment to optimize allocation of resources over present and future offspring</td>
</tr>
<tr>
<td>Upregulation of heat production</td>
<td>Regulation of heat production at a level that optimizes allocation of resources over present and future offspring</td>
</tr>
<tr>
<td>Increase milk production</td>
<td>Modulate milk production to optimize allocation of resources over present and future offspring</td>
</tr>
<tr>
<td>Induced maternal tolerance. Evade detection and destruction by maternal immune system</td>
<td>Tolerate semi-allogeneic fetal material. Eliminate fetal cells that upregulate resource transfer to levels not consistent with optimized allocation of resources over present and future offspring</td>
</tr>
</tbody>
</table>

In my beginning is my end...

Four Quartets

Thomas S. Eliot
What is life? (E. Schrödinger)

Le cinque grandi idee della biologia e della medicina (P. Nurse)
What is life? (E. Schrödinger)

Le cinque grandi idee della biologia e della medicina (P. Nurse)
Reduced brachial flow-mediated vasodilation in young adult ex extremely low birth weight preterm: a condition predictive of increased cardiovascular risk?

P. P. BASSAREO1, V. FANOS2, M. PUDDU3, P. DEMURU1, F. CADEDDU1, M. BAEZARINI1, & G. MERCURO1

1Department of Cardiovascular and Neurological Sciences, University of Cagliari, Cagliari, Italy and 2Department of Pediatrics and Clinical Medicine, Section of Neonatal Intensive Care Unit, University of Cagliari, Cagliari, Italy

(Received 5 July 2010; revised 27 July 2010; accepted 30 July 2010)

Figure 2. Relationship between flow-mediated vasodilation (FMD) and birth weight.
Could ADMA levels in young adults born preterm predict an early endothelial dysfunction?

P.P. Bassareo a,*, M. Puddu b, G. Flore a, M. Deidda a, E. Manconi a, A. Melis b, Y. Fanos b, G. Mercuro a

a Department of Cardiovascular and Neurological Sciences, University of Cagliari, Cagliari, Italy
b Department of Pediatrics and Critical Medicine, Section of Neonatal Intensive Care Unit, University of Cagliari, Cagliari, Italy

Fig. 1. Relationship between ADMA and birth weight.
This is what we are: lots and lots of connections.

“cells that fire together, wire together”
In collaboration with Utrecht and Padua Universities and Alessandria Hospital

Metabolomics in newborns with intrauterine growth retardation (IUGR): urine reveals markers of metabolic syndrome

Angelica Dossi1, Luigi Atzori2, Antonino Noto1, Gerard Hille Adrian Visser3, Diego Gazzolo4, Vincenzo Zanardo5, Luigi Barberini6, Anna De Magistris7, Melania Puddu1, Giovanni Ottolenghi5, Alessandra Atzel1, Milena Lussu6, Paola Carrina Murgia1 & Vagelios Fanos1

1Neonatal Intensive Care Unit, Perinatology Institute and Neonatal Section, University of Cagliari, Italy. 2Department of Obstetrics and Gynaecology, University Hospital, Utrecht, The Netherlands. 3Department of Maternal, Fetal and Neonatal Medicine, C. Amigo Children’s Hospital, Alessandria, Italy. 4Department of Paediatrics, University of Padua, Padua, Italy. 5Department of Neurobiological Sciences, University of Cagliari, Italy, and 6Department of Toxicology, University of Cagliari, Italy.
1H-NMR urine samples

Control Newborn

IUGR Newborn

6 VIP: creatinine, creatine, myoinositol, betaine, succinate, sarcosine.
Intrauterine growth restriction is associated with persistent aortic wall thickening and glomerular proteinuria during infancy

Vincenzo Zanardo, Tiziana Panelli, Gary Weiner, Vassilios Fanos, Martina Zaninotto, Silvia Visentin, Francesco Cavallin, Daniele Trevisanuto, and Erich Cosmi

1Department of Pediatrics, University of Padua, Padua, Italy; 2Institute of Gynecology and Reproductive Sciences, University of Padua, Padua, Italy; 3Neonatal-Perinatal Medicine, St. Joseph Mercy Hospital Ann Arbor, Ann Arbor, Michigan, USA; 4Puericultura Institute, University of Cagliari, Cagliari, Italy; and 5Laboratory Medicine Department, University of Padua, Padua, Italy