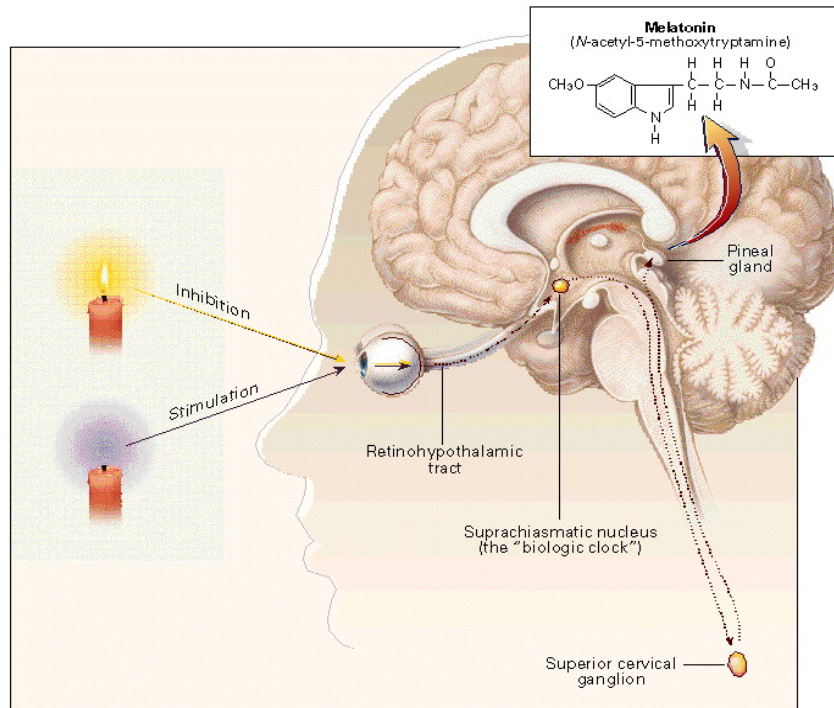


Anti-inflammatory therapies: TBI

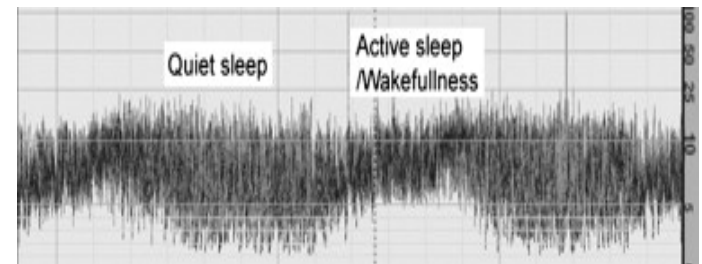
- Persistent neuroinflammation can cause progressive neurodegeneration that may be treatable even weeks after traumatic injury.
- Animal models
 - reducing inflammation after repeated mild brain injury in rats leads to improved behavioural outcomes and anti CD11b therapy reduces neuroinflammation
 - Shultz SR et al., 2013
- Erthrypoietin has also shown benefit in animal models
 - Zhu L et al., 2009
- Melatonin
 - anti-inflammatory and anti-oxidative effects
 - may also improve the disruption of the sleep wake cycle and circadian patterns
 - An ongoing RCT is studying melatonin as a treatment for post-concussive syndrome in children
 - Barlow KM et al., 2014

Circadian Rhythm

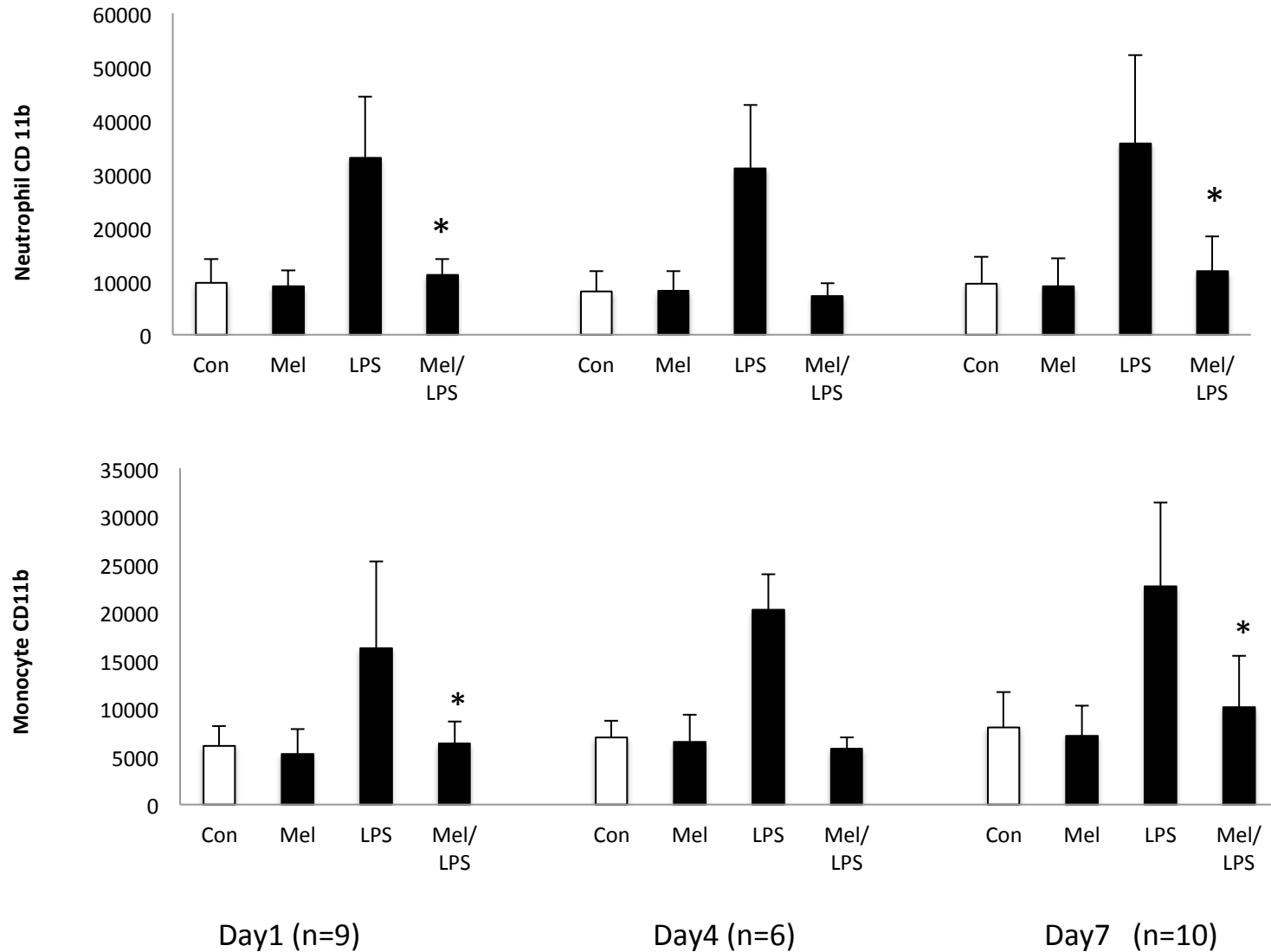


Brzezinski A. N Engl J Med 1997;336:186-195.

- Altered sleep-wake cycle in infants with brain injury
- Decreased early morning melatonin compared with controls
- Altered neutrophil function with melatonin in vitro



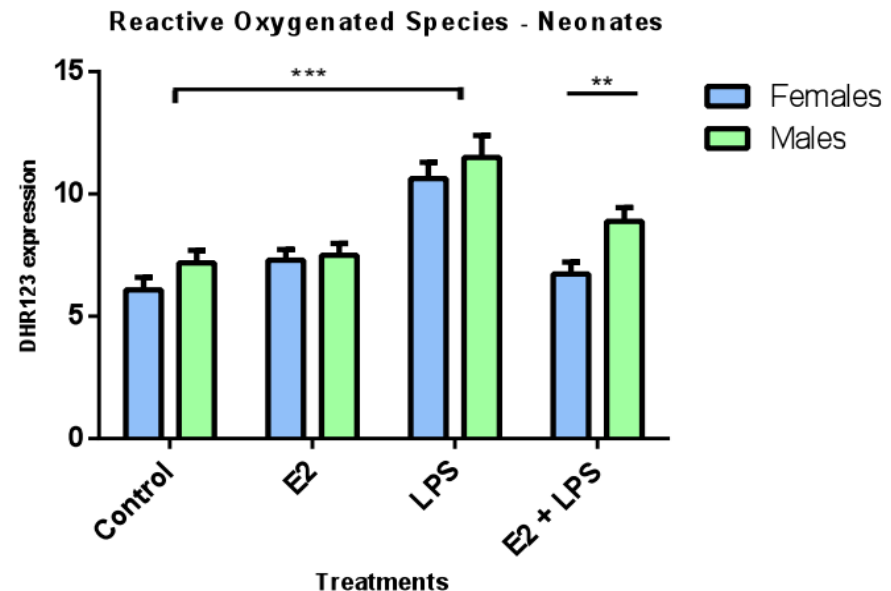
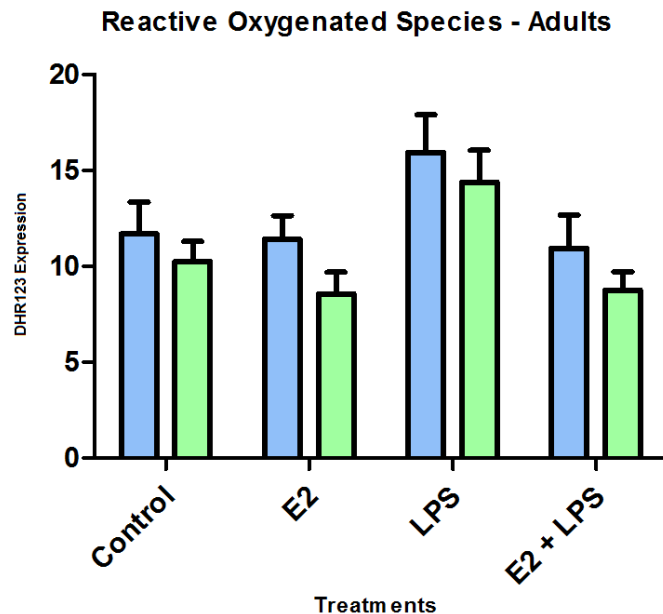
Melatonin reduces neutrophil CD11b in the presence of LPS



Gender Disparity in Immune Function

CD11b, ER- α , and ER- β levels showed no difference in male vs female neonates however all levels were reduced in male vs female adults.

E2-mediated inhibition of LPS-induced ROS is more pronounced in female neonates... not adults

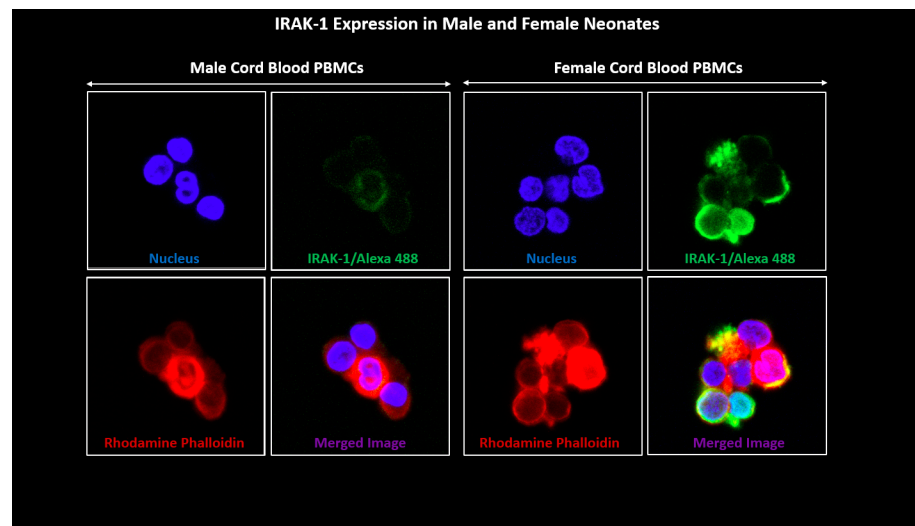
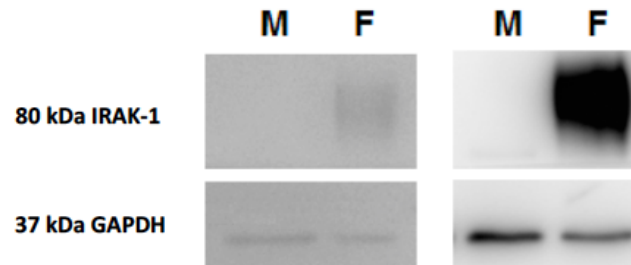
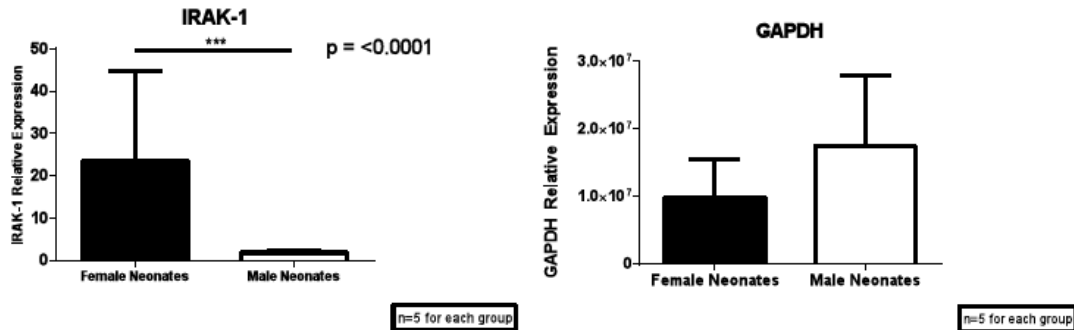


O'Driscoll D. N., Kelly L. A., McKiernan P. J., Greene C. M., Eleanor J. Molloy.

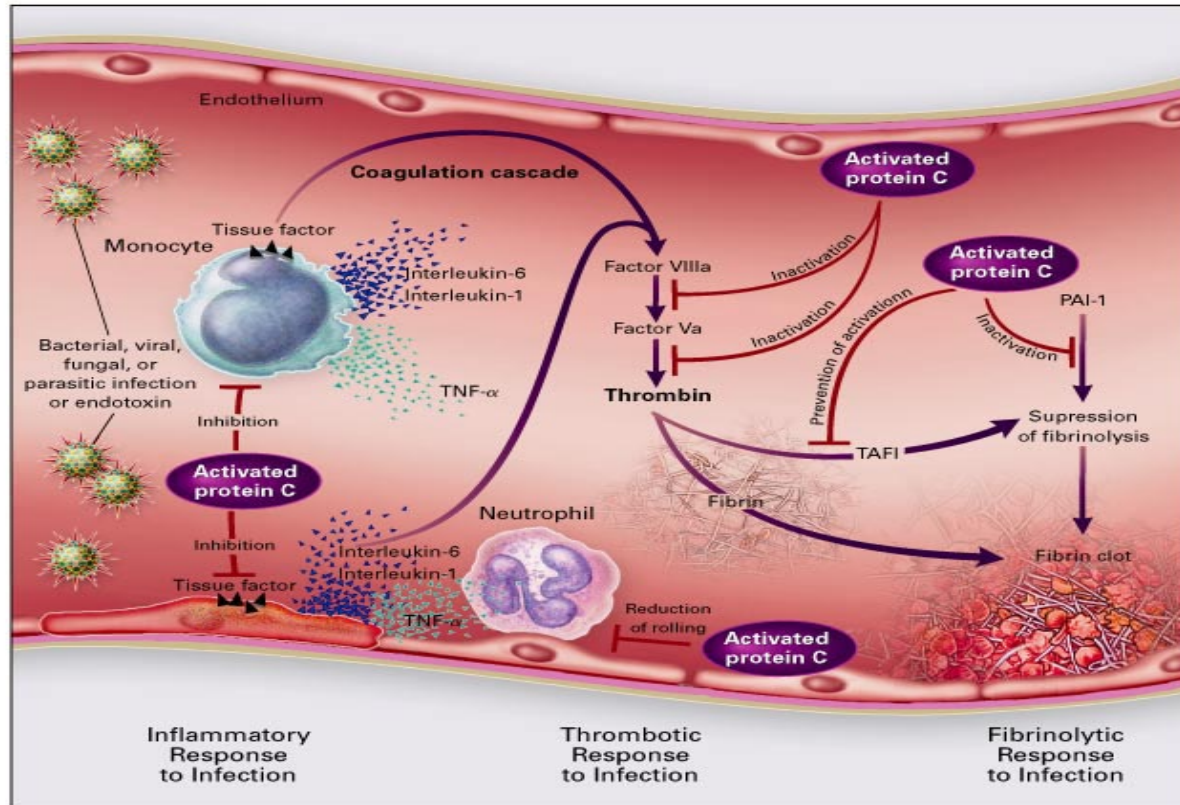


IRAK-1 (Xq28t) is expressed at significantly higher protein level in female versus male neonates

Western Blot:



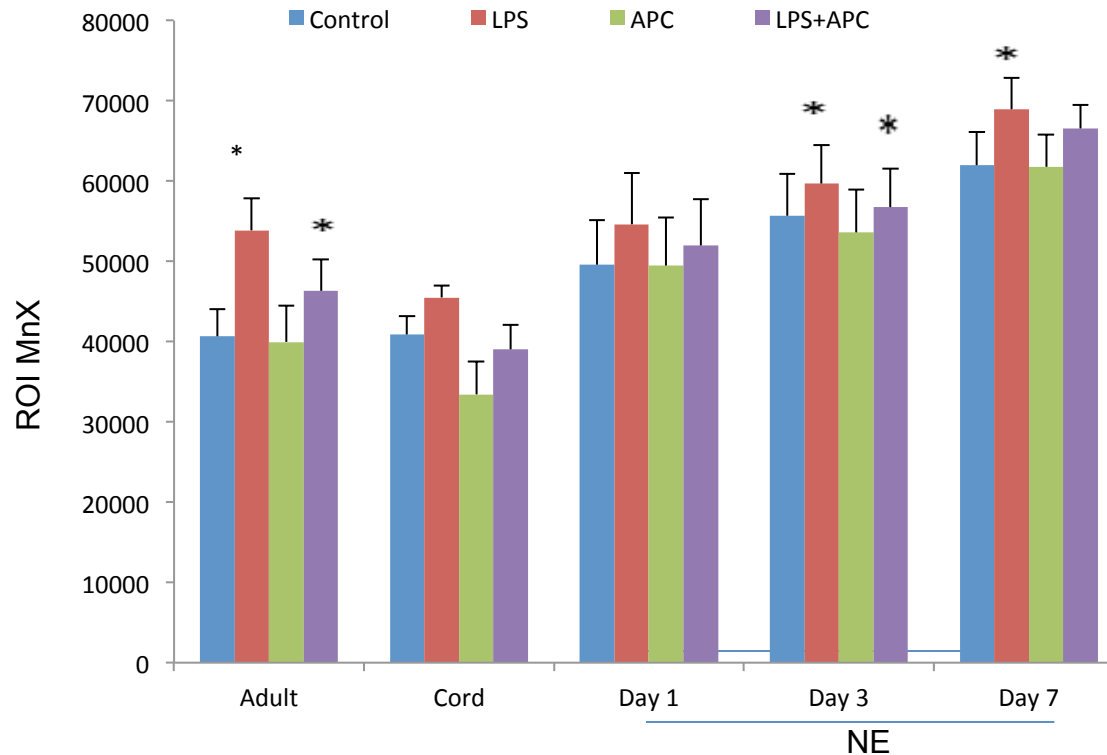
Activated Protein C (APC) and inflammation



Bernard GR, et al, *NEJM*, 2001, 344:699

Neonatal encephalopathy

Activated protein C reduced LPS-induced neutrophil TLR4 and ROI on day 3

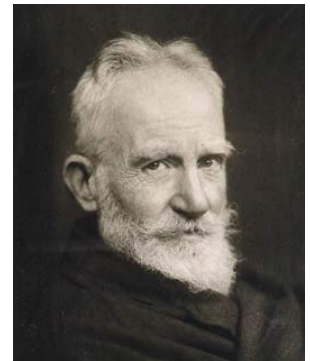


- ❑ Neutrophil ROI baseline was higher in NE infants versus adults and cord controls.

Individualised immunotherapy

The Doctors Dilemma

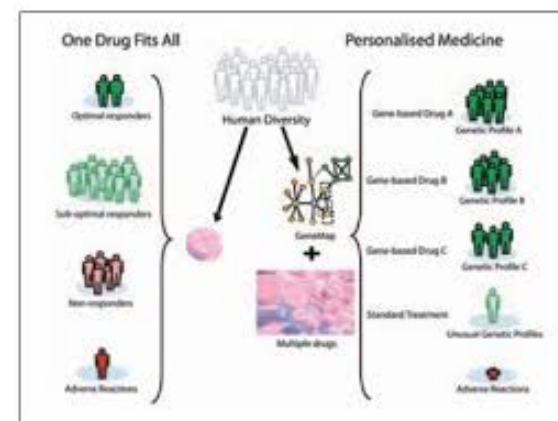
- Opsonin index
 - “Send a drop of the patient's blood to the laboratory at St. Anne's; and in fifteen minutes I'll give you his opsonin index in figures.
 - If the figure is one, inoculate and cure: if it's under point eight, inoculate and kill.”
 - “To inject a vaccine into a patient without first testing his opsonin is as near murder as a respectable practitioner can get”.



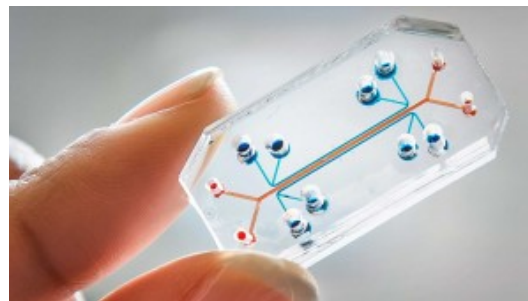
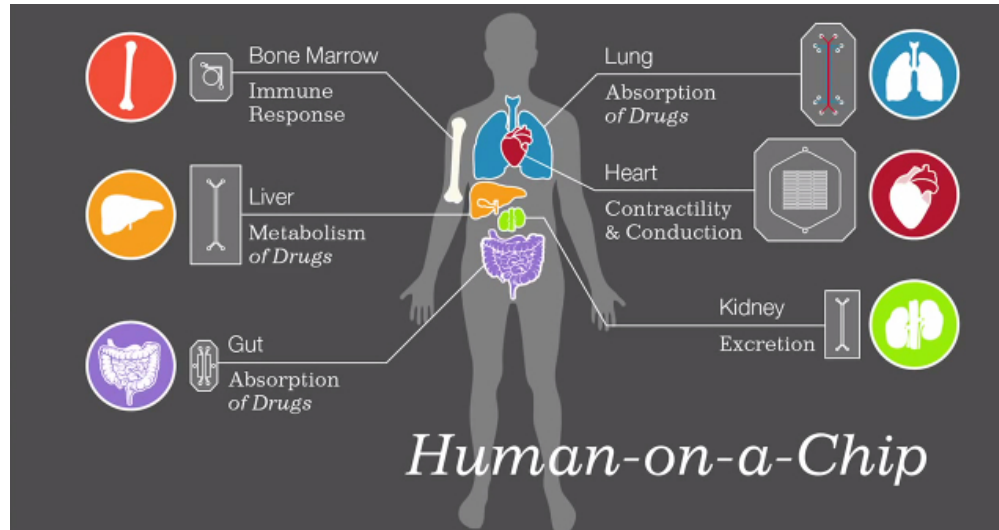
Personalised Medicine



Genotype specific
therapies
e.g. CF, Breast Ca



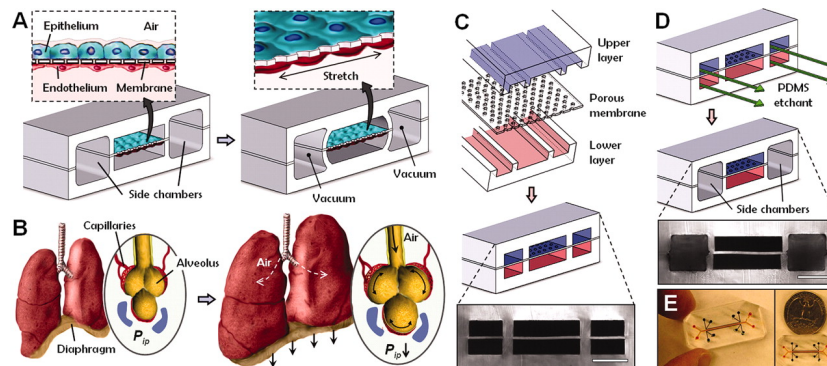
Nanotechnology



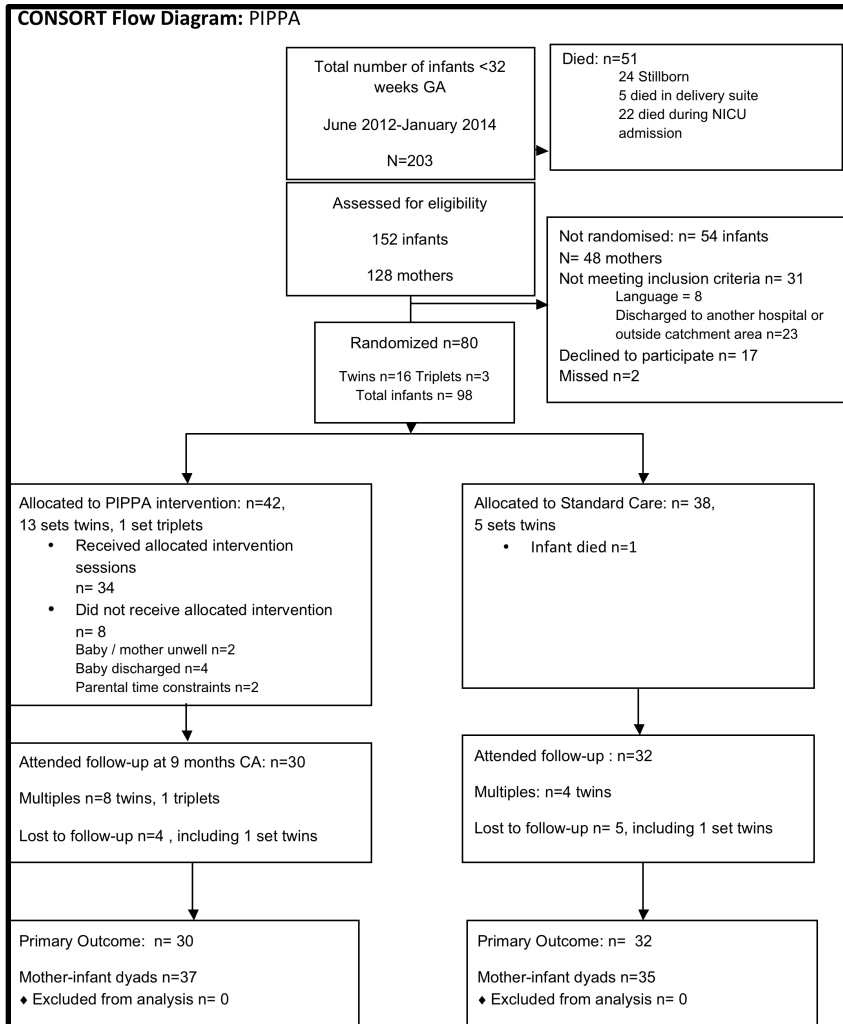
<http://www.elveflow.com/a-review-about-organs-on-chip>

Nanotechnology in medicine

- Nanoparticles for drug delivery directly to cancer cells or vaccine development
- Organ on a chip may remove need for animal models esp drug studies
- Drugs that cross blood brain barrier



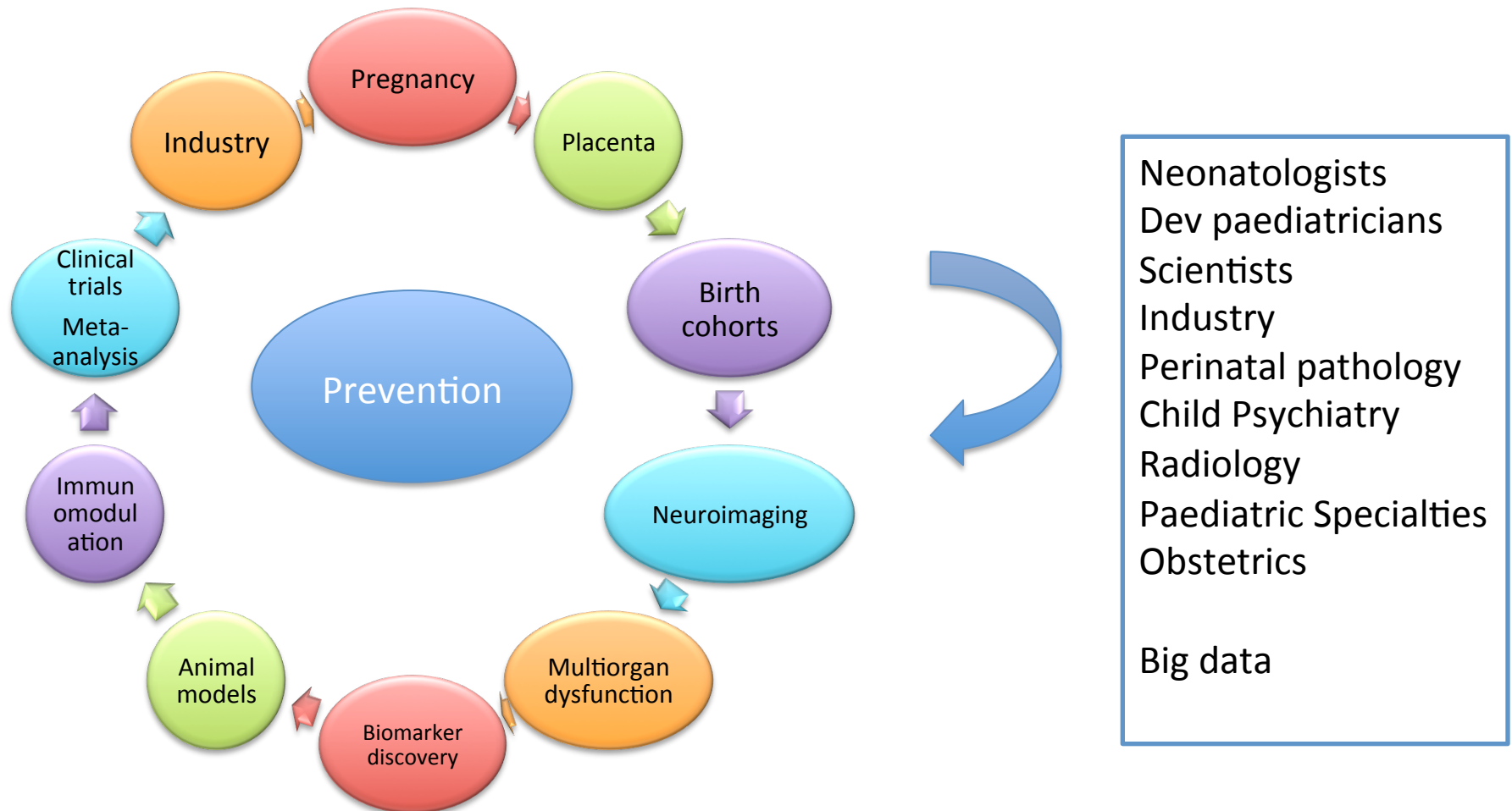
Preterm-Infant Parent Programme for Attachment PIPPA



Infants in the intervention group
had significantly fewer
communication problems at 12
months corrected age

Twohig A, McCarthy A, O'Donnell CP
Smyke A, Wai Wan M, McNicholas F, Molloy EJ

Collaborative Multidisciplinary Network of Neonatal Brain injury



Neonatal Brain injury

Databases

CP, Vermont-Oxford,
National Perinatal Epi

Neurodev.

EEG

MRI

Organ-specific
Biomarkers

Followup

Population

Translational

NBI

Clinical
MODS

Basic laboratory

Inflammatory
Markers &
Stem cell
responses

Lifecycle Research

- GUI=>TILDA
- Downs Syndrome:
 - Model for lifecycle research in TCD
 - Masterclass RCPI Prenatal to Old Age
 - Multidisciplinary & multiorgan
 - Brain health throughout life



Summary so far

- Babies and children with brain injury have abnormal immune function that persists after the initial insults
- This provides a target for treatment but need to individualize to each patient
- Multidisciplinary, multiorgan, lifecycle research
- *“Most discoveries are made regularly every 15 years: and its fully a hundred and fifty since yours was last made. That’s something to be proud of. But your discovery’s not new....” GB Shaw*

Child Health Research



Ireland: Challenges

- Number of paediatricians per child
 - 10th of EU and USA
- Scheduled physical exams in childhood
 - 2 v 21 in USA
- Legislation on TOP
- Disability
 - 48,000 children ; 11 consultants
- Child protection
 - 4 consultants



European Academy of Paediatrics

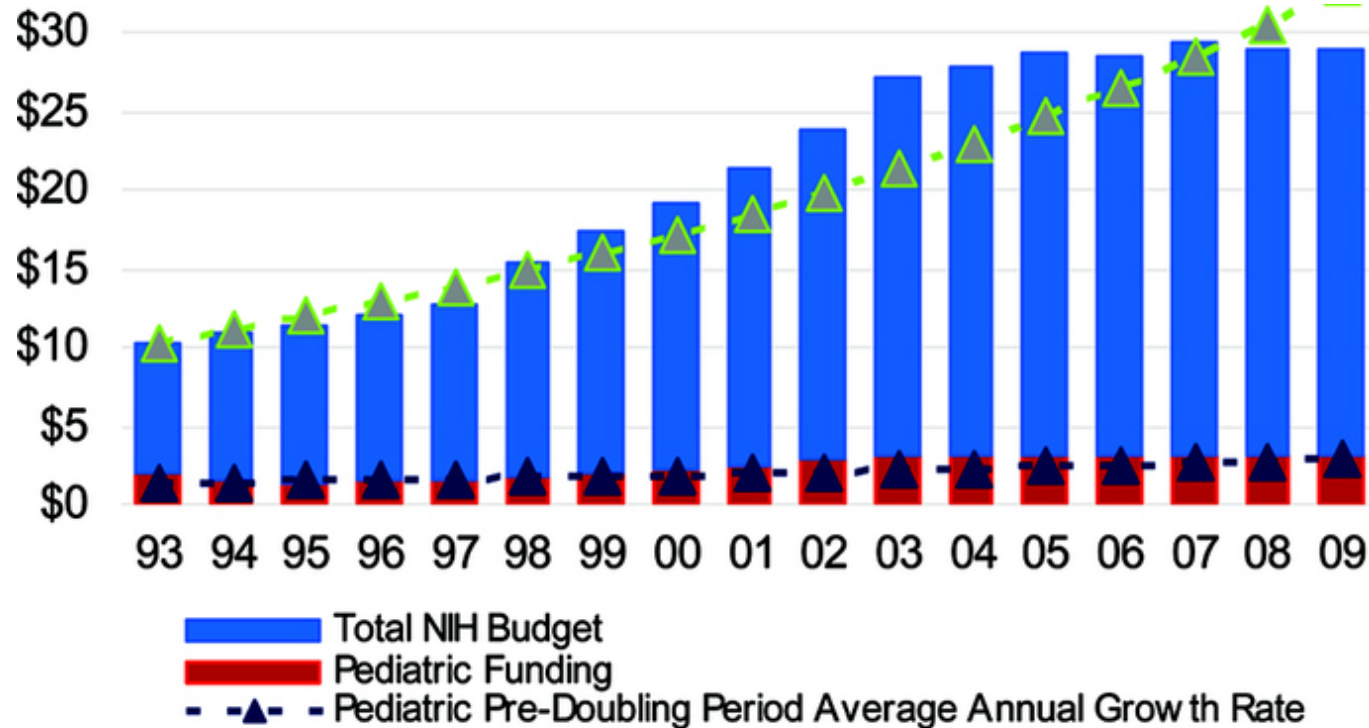
Paediatric Section of U.E.M.S.
Union Européenne des Médecins Spécialistes



Inequality: Adults versus Children

- Funding:
 - Representation on funding bodies
 - 6/500 MRC & Wellcome Trust
 - Turning the Tide, RCPCH 2012
- Pharmaceutical industry
 - Medicines for children
 - Biologics
- Number of academics
 - 10.2% decrease v 32% increase: RCPCH
- Smallest patient, smallest resources
 - NICU patient 1/100th cost of adult cardiac intensive care

That Sinking Feeling, Again?



**The State of National Institutes of Health Pediatric Research Funding, Fiscal Year
1992–2010**

Daniel P Gitterman and William W Hay Jr, Ped Res 2010

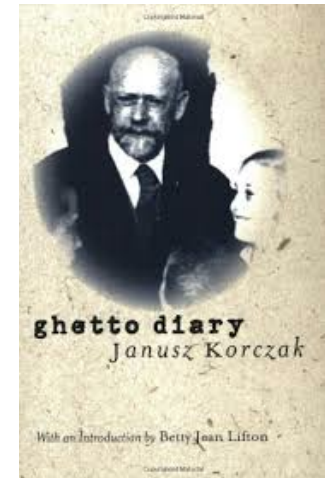
UN Rights of the Child

“Children are not the people of tomorrow, but people today. They are entitled to be taken seriously. They have a right to be treated by adults with tenderness and respect, as equals. They should be allowed to grow into whoever they were meant to be - The unknown person inside each of them is the hope for the future.”

Janusz Korszak pen name: Henryk Goldszmit

Paediatrician, Children's author, Polish-Jewish educator

Died in Treblinka with 192 children from his Warsaw orphanage



The Future

- New National Paediatric hospital, SJH



"I have been assured by a very knowing American of my acquaintance in London, that a young healthy child well nursed is at a year old a most delicious, nourishing, and wholesome food, whether stewed, roasted, baked, or boiled ..."

A Modest Proposal, 1729, Dean Swift

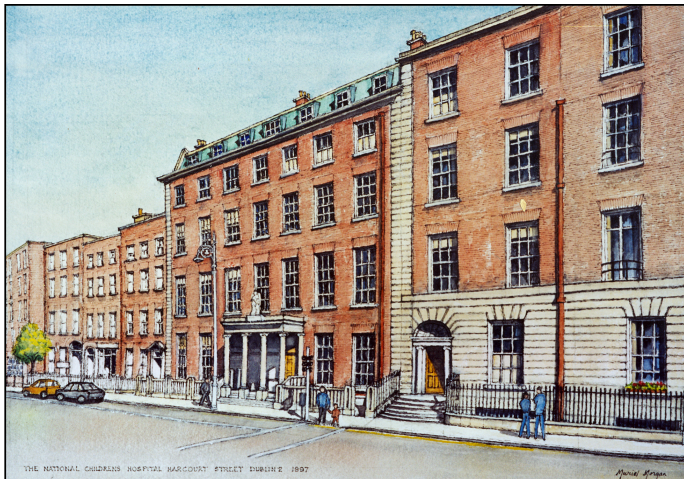
Foundling hospital, 1727

52,150 admitted x 30y:

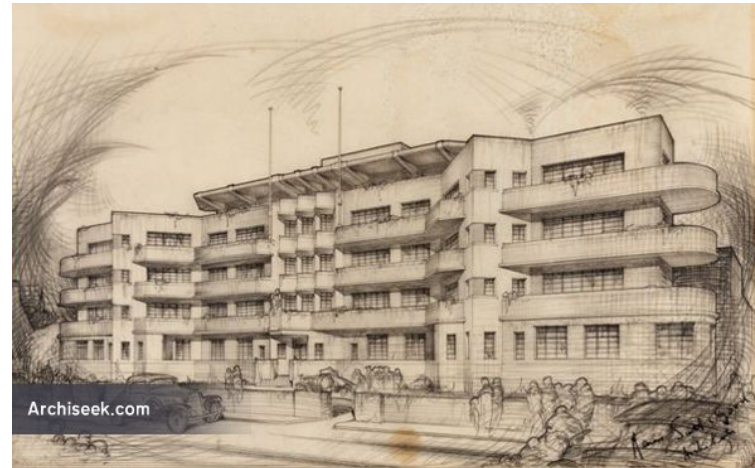
41,2524 died ~ 80%

The Future

- New National Paediatric Hospital, SJH 2020



National Children's Hospital,
Harcourt St, 1821
1st in British Isles



Scott & Good; unbuilt plan for St
Ultans, 1936
Dr. Kathleen Lynn

New National Paediatric hospital, SJH



Vital: CRIC and Maternity



National Paediatric Hospital Project - Children's Research & Innovation Centre

VIEW OF MAIN ENTRANCE - COURTYARD



Funding

- National
 - NCRC / CUH / NCH
 - HRB/ MRCG/SFI
 - Wellcome
 - MD/PhD
- International
 - Horizon 2020
 - NIH
- Philanthropy
- SFI



Turning the Tide: Harnessing the power of child health research: 2012

RCPCH

Royal College of
Paediatrics and Child Health

Leading the way in Children's Health



Paediatric and Child Health Research in Ireland

- Data difficult to access: Estimate...
- 2006-2016
 - > 70 Paediatricians: MD/PhD in Ireland
 - ~also 5-10 MD overseas
 - > 25 currently doing MD/PhD in Ireland
 - Many more in Child Health

- Publications
 - > 200 in 2016: OLCH...underestimate



Children's Forum=>TRICC

- TCD researchers in Childhood:
 - n>100
 - All Faculties and Institutes:
 - TTMI, CRANN, TCIN, TLRH
 - Translational Paediatrics Group
 - TCD Research in Childhood Centre:
 - TRICC
- Nationally
 - HRB Mother and Baby Network
 - National Paediatric Network: IPCRIN
 - National Perinatal Epidemiology Centre



International collaborations

Research and policy

- General and Adolescent Paediatric Research Collaborative-UK :GAPR-UKI
- RCPCH/ APA
- SPR/APS
- ESPR
- Emergency medicine/Haematology/Oncology/
Respiratory/ Genetics/Child Psychiatry/
Neonatal cardiology.....

Students

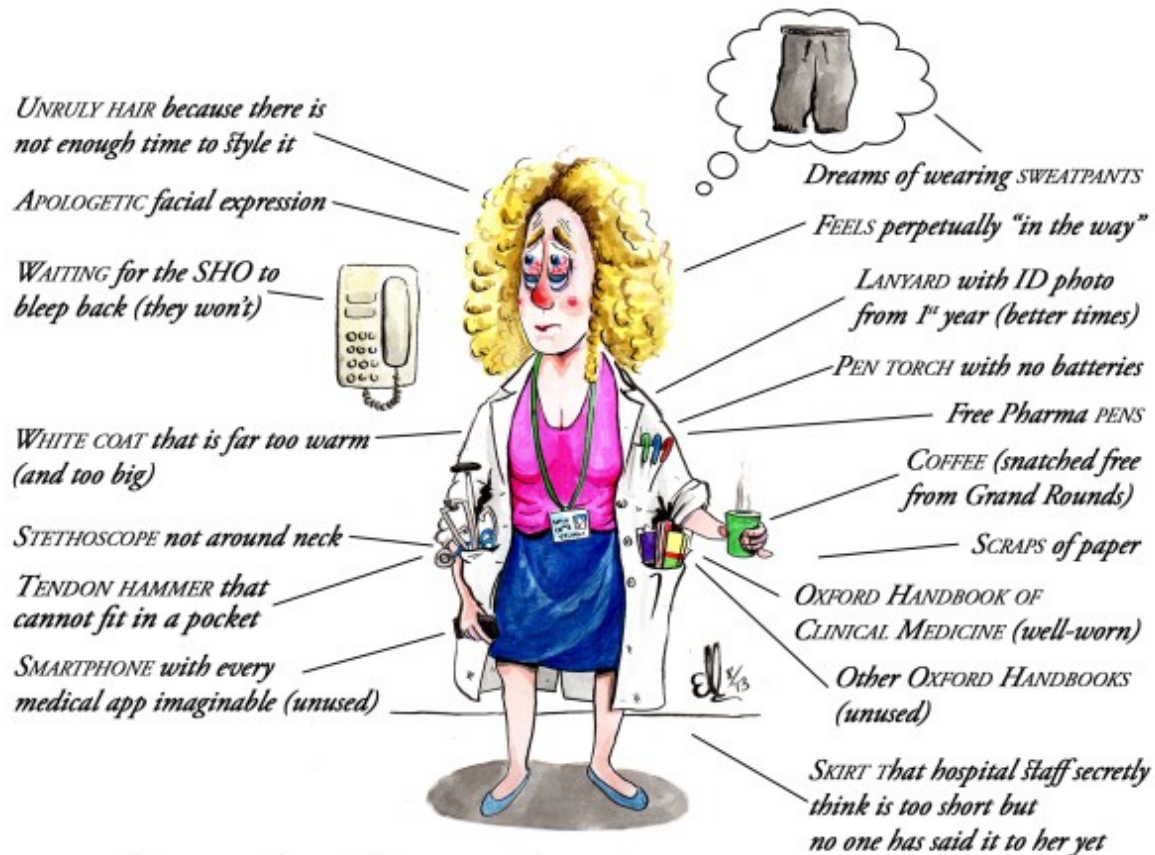


Figure of a MEDICAL STUDENT

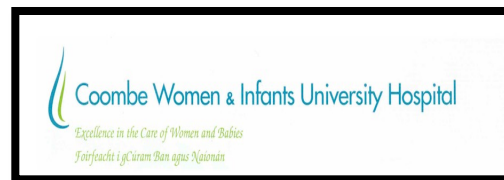


The Class of 2013 graduate

<http://einkelleher.com/portfolio/graduation-season/>

Medical student of 2016

- Role models, mentoring and career development
- Quality improvement initiatives
- Simulation: high and low fidelity
- EBM projects
- Interdisciplinary education and team work
 - Global child health
 - Geoghegan S et al., Ir Med J. 2015 Jul-Aug;108(7):194.
 - Preventative health
 - Palliative care
 - Disability: Complex needs
 - PICU
 - Children literature
 - Ethics and Law in Child Health
- National Paediatric Curriculum



Discipline of Paediatrics & Child Health

- Paediatric (Childrens) Society
- Career advice
- Finals!
- Postgrads
 - Gen Academic Paeds
 - MD/PhD programme
 - RCPI



Discipline of Paediatrics & Child Health



Trinity College
The University of Dublin

Parents and Children

Academic Staff:

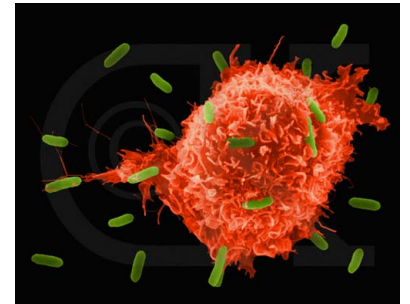
Ms. Sioban Tynan-Omahony	Ms. Sandra Archbold	Ms. Anna Lambe	
Professor Edna Roche	Dr Judith Meehan	Dr Nehad Metwally	Dr Murwan Omar

Clinical Senior Lecturers & Professors:

Professor Eileen Treacy	Professor Hilary Hoey	Dr Michael Capra	Dr Declan Cody
Dr Corrina McMahon	Mr Fergal Quinn	Dr Brendan O'Hare	Dr Basil Elnazir
Dr Rosemarie Manning	Dr Peter Greally	Dr Colin McMahon	Professor Paul McNally
Dr David Coghlan	Mr John Gillick	Dr Emma Curtis	Dr Ciara McDonnell
Dr Aideen Byrne	Dr Grainne O'Regan	Dr Angela Byrne	Dr John Kelleher
Dr Aisling Snow	Dr Jan Miletin	Mr Brian Sweeney	Dr Patrick Gavin
Dr Denis McDonald	Dr David Corcoran	Dr Sean Walsh	Dr Aengus O Marcaigh
Dr David Webb	Mr David Orr	Dr Shoana Quinn	Dr Ciara Martin
Elaine O'Mullane	Fiona McGrane	Dr Turlough Bolger	Dr Stanley Koe
Prof. Carlos Blanco	Dr David Coleman	Dr Margaret Sheridan-Pereira	
Dr. Victoria McEneaney	Dr. Lynne Kelly	Mr G. Lakahmanadas	
Dr Joanne Balfe	Mr John Caird	Dr Suzanne Crowe	Dr Martina Healy
Dr John Kelleher	Mr Sri Paran	Dr Jane Pears	Dr Ethne Phelan
Dr AnneMarie Broderick	Dr Maureen Connolly	Dr Colm Costigan	Dr Brendan Doody
Prof Ray Fitzgerald	Mr Esmond Fogarty	Prof Alan Irvine	Dr Hugh Monaghan
Dr Beatrice Nolan	Dr Paul Oslizlok	Dr Kevin Walsh	Dr Carol Blackburn
Prof Billy Bourke	Dr Michelle Clifford	Mr Darach Crimmins	Dr Ciara Farrell
Prof Andrew Green	Ms Marie Roddy	Mr Patrick Kiely	Dr Nadeem Gadelsayd

Summary

- Challenges
 - Funding
 - Inequality for children
- Short term solutions
 - Translation Research to Clinical practice
 - Mapping research in Ireland
- The Future
 - National Paediatric hospital
 - National & international Networks



Collaborators

National Maternity Hospital

- Roberta McCarthy
- Helen Walsh
- Prof John Murphy
- Prof Colm O'Donnell
- Dr. Anne Twomey
- Hilda Wall
- Prof Rhona Mahony
- Dr. Paul Downey
- Dr. Eoin Mooney
- Eoghan Hayden
- Dr. Susan Knowles



Prof Ger Boylan, UCC
Prof O'Gorman, UL

Coombe Womens & Infants University Hospital

- Dr. Margaret Sheridan-Pereira
- Julie Grantham-Sloan
- Prof Sean Daly
- Dr. Jan Miletin
- Dr. Jana Semberova
- Prof. Martin White
- Dr. John Kelleher
- Anne O'Sullivan
- Dr. Pamela O'Connor

RCSI/Rotunda

- Dr. Afif El-Khuffash
- Prof Catherine Greene
- Dr. Eva Jiminez-Mateos
- Dr. Breda Hayes
- Prof Mary King
- Prof D Kenny
- Prof Alf Nicholson
- Prof Naomi McCallion
- Prof Adrienne Foran
- Dr. Wendy Ferguson

TCD

- Prof John O'Leary
- Prof. D Doherty
- Dr. Sarah Doyle
- Prof Mark Little
- Prof Arun Bodke
- Prof Veronica O'Keane
- Prof Luke O'Neill
- Dr. Annie Curtis
- Dr. Nigel Stevenson
- Dr. Denise McDonald
- Dr. Orla Franklin

UCD

- Prof Bill Watson
- Dr. Amanda O'Neill
- Prof Fionnuala McAuliffe
- Dr. Eoin Cummins
- Prof Nuala Murphy
- Prof Fiona McNicholas
- Dr. Irene Regan
- Dr. Brian Philbin
- Dr. Beatrice Nolan
- Prof Owen Smith
- Dr. Ellen Crushell

PhD/MD/MSc students

- Dr. Afif El-Khuffash
- Dr. Fiona O'Hare
- Dr. Katie Armstrong
- Dr. Hassan Eliwan
- Dr. Deirdre Sweetman
- Dr. Jean Donnelly
- Dr. Aoife Twohig
- Dr. Saima Aslam
- Dr. Zunera Zareen
- Dr. Murwan Omer
- Dr. Mary O'Dea
- Eoghan Hayden
- Catherine Doughty
- Dr. Joseph Chukwu

Postdoctoral fellows

- Dr. Victoria McEneaney
- Dr. Lynne Kelly





"A happy family is but an earlier heaven."
GBS







Pictures of 23 week girl I the first few days of life
Removed for patient confidentiality

Pictures of 23 week girl I the first few weeks of life
Removed for patient confidentiality

Pictures of 23 week girl at 2 years on discharge from followup clinic
Removed for patient confidentiality

Goodbye

Pictures of 24 weeker twins at 2 years on discharge from followup clinic
Removed for patient confidentiality

Thankyou



“Life is a flame that is always burning itself out, but it catches fire again every time a child is born.” George Bernard Shaw

Shaw's Immunological legacy

- “buttering” =Opsonization=IVIg
- “manufacture of that butter..... goes on...by ups and downs” =SIRS/CARS
- “Inoculate... in negative phase and you kill”
=Immunosuppression
- “Stimulate the phagocytes” =e.g.GCSF
- “Drugs are a delusion” = antibiotic resistance
- Opsonin index=individualised immunotherapy