ARCHITETTURA DELLA RICERCA

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“Cosa stai cercando”
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RICERCA BIOMEDICA

• Osservazionale
• Sperimentale
THE ORIGIN OF SPECIES

BY MEANS OF NATURAL SELECTION,

IN THE

PERFECTION OF KINRED RACES IN THE STRUGGLE FOR LIFE.

By CHARLES DARWIN, M.A.,

PROFESSOR OF ZOOLOGY IN THE UNIVERSITY OF EDINBURGH.

LONDON,

JOHN MURRAY, ALBEMARLE STREET.

1859.
Macro-evolution
Problemi posti dalla pratica clinica

Nuovi portati dalla ricerca di base
PROGETTO DI RICERCA

• Delineare il progetto: obiettivi e criteri di importanza scientifica
• Elaborazione: letteratura, metodologie, piano sperimentale, considerazioni statistiche
• Preventivo economico
• Principi etici e Comitato Etico
• Realizzazione del progetto
• Rendicontazione scientifica
• Rendicontazione economica
Hemoglobinuria:
Sometimes Paroxysmal, Sometimes Nocturnal
Paroxysmal Nocturnal Hemoglobinuria (PNH) is an acquired disorder defined by a clinical triad:

- Intravascular Hemolysis
- Thrombosis
- Cytopenias
Ham Test in a PNH Patient

Control RBC

Patient RBC
CLONAL ORIGIN OF PNH CELLS IN A G6PD A/B HETEROZYGOTE PATIENT

University College Hospital
Ibadan, Nigeria
Mechanism of Action of CD59

adapted from: Meri et al, 1990

with CD59

C5b-8

\[ C9 \] loosely bound (displaceable)

CD59

C9

\[ 4^\circ C \]

C9 tightly bound (not displaceable)

CD59

C9

\[ 37^\circ C \]

without CD59

C5b-8

\[ C9 \]

C9

\[ 4^\circ C \] loosely bound (displaceable)

C9

\[ 37^\circ C \] tightly bound (not displaceable)

adapted from: Meri et al, 1990

C5b-8

\[ Poly-C9 \]
Proteins Deficient on PNH Blood Cells

Hematopoietic Stem Cell

RBC

Platelets

PMN

Monocytes

B cells

CD24
CD55
CD58*
CD59
CD73
CD48
CD90
PrPc

CD16*

T cells

CD55
CD58*
CD59
CD48
ADP-RT
CD73
CD10

NK cells

CD55
CD58*
CD59
CD48

CD16*

all these proteins are GPI-linked

CD14
CD55
CD58*
CD87
CD109
PrPc
GPI-80

CD66b
CD109
CD157
LAPNB1
ADP-RT
CD50
CD108
CDw52
CDw108
PrPc
Group 8

CD55
CD58*
CD59
CD48
CD16*

CD55
CD58*
CD59
CD109

CD16*

CD55
CD58*
CD59
CD109

CD16*

CD55
CD58*
CD59
CD109

CD16*

CD55
CD58*
CD59
CD109

CD16*

CD55
CD58*
CD59
CD109

CD16*
THE BIOSYNTHETIC PATHWAY OF THE GPI ANCHOR INVOLVES AT LEAST TEN DISCRETE STEPS

[From Kinoshita et al., J Biochem (JPN) 144:287, 2008]
Emoglobinuria Parossistica Notturna (EPN) Patogenesi

Cellula Staminale Ematopoietica
Mutations in the PIG-A Gene

- Large deletions
  - del 735 bp
  - del exons 3-4-5

- Null mutations
  - 1
  - 2
  - 3
  - 4
  - 5
  - 6

- Non-null mutations
  - Aval polymorphism
  - 50 bp

- Mutations in the PIG-A Gene
A. Normal, steady state

A normal (CD55+, CD59+) red cell can cope with the threat of complement activation

(From Luzzatto, Risitano & Notaro, 2010)
B. PNH, steady state

An abnormal (CD55-, CD59-) red cell (PNH red cell) will be lysed sooner or later by activated complement

(From Luzzatto, Risitano & Notaro, 2010)
TARGETING THE COMPLEMENT CASCADE

**Classical Pathway**
- Activator: Antibody/Antigen Complexes
- Key Enzymes: C1q, C1r, C1s, C4, C2
- Initial Complex: C4b2a3b
- Final Complex: C5b-9
- Functions: Lysis, Cell Activation, Chemotaxis

**Alternative Pathway**
- Activator: Microbiological Membranes (Bacterial LPS), Immune Complexes, Mammalian Cell Membranes
- Key Enzymes: Factor B, Factor D, C3b Bb
- Initial Complex: C3bBb3b
- Final Complex: C5b-9
- Functions: Lysis, Cell Activation

**Lectin Pathway**
- Activator: MBL
- Key Enzymes: C4, C2
- Initial Complex: C4b2a
- Functions: Lysis, Cell Activation

**Potent Anaphylatoxin**
- C3a, C5a, C5b
- Functions: Chemotaxis, Cell Activation

**Immune Complex and Microbial Opsonization**
- Initial Complex: C3b, C3b-Bb3b
- Functions: Lysis, Cell Activation

**Anti-C5 (ECULIZUMAB)**
- Functions: Inhibits C5 convertase, Prevents terminal complement complex formation, Reduces inflammation, Lysis, Cell Activation
Eculizumab (anti-C5 antibody)

- Human framework regions
- Complementarity determining regions (murine origin)
- Human IgG4 heavy chain constant regions 2 and 3
- Human IgG2 heavy chain constant region 1 and hinge

Complementarity determining regions (murine origin)
ECULIZUMAB ARRESTS THE SELECTIVE INTRAVASCULAR LYSIS OF PNH III RED CELLS

ECULIZUMAB CAN ABROGATE THE NEED FOR BLOOD TRANSFUSION


(Placebo group) Eculizumab

No. at Risk
Placebo group 44 44 36 30 23 13 7 6 3 1 0 0 0 0 0 0 0
Eculizumab group 43 41 41 39 37 36 36 32 32 31 27 27 26 26 24 22

P<0.001

ECULIZUMAB HAS AN IMPACT ON THE QUALITY OF LIFE


ECULIZUMAB HAS AN IMPACT ON THE QUALITY OF LIFE (Hillmen et al., New Eng J Med 355:1233, 2006)
3D STRUCTURE OF THE EPIDERMAL GROWTH FACTOR RECEPTOR
THE IRESSA/LUNG CANCER STORY. I.

• Non-small cell lung cancer (NSCLC) is a major cause of death in many countries
• NSCLC over-express the epidermal growth factor receptor (EGFR) in 40-80% of cases
• Gefitinib (Iressa) is an inhibitor of the TyrKin activity of EGFR

(From Lynch et al., NEJM 350:2129,2004)
Response to Gefitinib in a Patient with Refractory Non–Small-Cell Lung Cancer

(From Lynch et al., NEJM 350:2129, 2004)
THE IRESSA/LUNG CANCER STORY. II.

- In a study at Mass General Hospital 25 out of 275 patients had an impressive clinical response to gefitinib.
- In 8 out of 9 responders in whom the $EGFR$ gene was sequenced a somatic mutation was found within the kinase domain.
- No mutations were found in 7 out of 7 non-responders.

(From Lynch et al., *NEJM* 350:2129, 2004)
RICERCA NEL SETTORE SALUTE

- Geografia
- Storia
- Tipologie
  - Epidemiologia
  - Prevenzione
  - Diagnosi
  - Cure
  - Procedure infermieristiche
  - Qualità di vita
  - Modalità somministrazione cure
  - Aspetti economici
PROGETTI ITT

- Ricerca sul CANCRO in TOSCANA
  - Cancer Research
  - Clinical Cancer Research
  - Epidemiology
  - Supportive care
- Università, Ospedali, CNR
- Peer review in due stadi: referees esterni, ISAB
- Progetti approvati
  - 2007: 25 su 85
  - 2009: 33 su 109
• Sydney BRENNER (Cambridge), Chair
• Dino AMADORI, Forlì
• Andrea ARDIZZONI, Parma
• Paolo BRUZZI, Genova
• Giannino DEL SAL, Trieste
• Jean-Claude Horiot, Genolier
• Pier Paolo PANDOLFI, Boston
• Robert PINEDO, Amsterdam
• Paolo VINEIS, London
NOMINA NUMINA
*(what’s in a name?)*

- Grant
- Principal investigator (PI)
- Post-doctoral Fellow (post-doc)
- Graduate Student
- Resident Fellow

- Finanziamento
- Titolare della ricerca (capo-cordata)
- Borsista; Co.co.co.; (precario)
- Dottorando
- Specializzando
- Specializzando
CLINICAL QUALITY CONTROLS made user friendly

MORTALITY AND MORBIDITY REVIEWS

- Regular periodicity
- Appropriate notice
- Mix of flagged and random cases
- Collegial
- Analysis carried out by an independent but internal colleague
- Frank discussion
- No attacks
- Experienced sensible chairman essential
ETHICAL and REGULATORY ISSUES IN THE CLINICAL USE OF STEM CELLS & GENE TRANSFER

• Compliance with Good Manufacturing Practice (GMP) standards
• Compliance with all rules and regulations on clinical trials
• Ethics Committee approval
An investigator involved in a clinical trial should not have any financial interests in any aspect of the trial itself.

American Society of Gene Therapy. 1999
STEPS IN CANCER MANAGEMENT

- Diagnosis
- Staging
- Radical treatment
- Surveillance of remission
- Treatment of relapse
- Salvage treatment
- Management of patient with advanced cancer
LA COMUNICAZIONE
CON I PAZIENTI CON TUMORI

• Dire/non dire
• Quanto dire
• Quando dire
• Comunicazione con familiari
• Comunicazione con paziente
• Comunicazione e sostegno psicologico
CAPIRE, CURARE. PREVENIRE IL CANCRO AL MEGLIO PER TUTTI

www.ittumori.it