Il cervello che cambia
9 novembre 2019

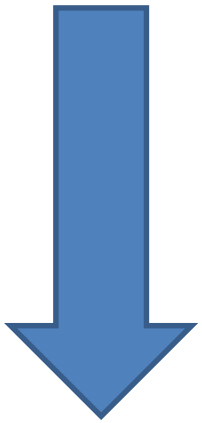
Recenti avanzamenti e frontiere di ricerca in…
Anatomia e istologia patologica

Direttore J.L. Ravetti, Dott. G. Gaggero

- Istopatologia
- Molecolare
- Gestione/organizzazione
- Il «passato» nel presente e nel futuro

- Istopatologia
- Molecolare
- Gestione/organizzazione
- Il «passato» nel presente e nel futuro

Biomarkers in vivo



Markers applicazione istologica

MALATTIE NEURODEGENERATIVE

- Perdita neuroni
- Accumulo proteine

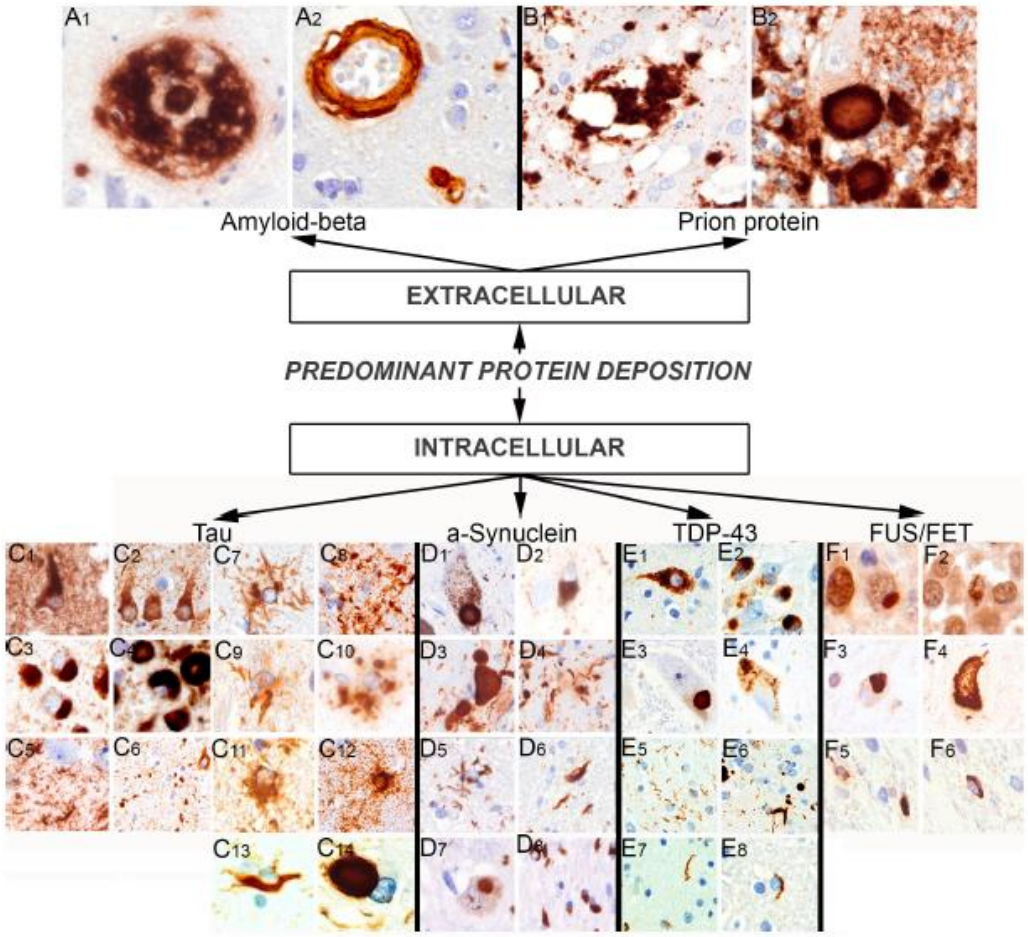
Laddove presenti, i markers istologici hanno significato di:

- validazione di effettiva presenza di accumulo proteico
- definizione del tipo proteico
- classificazione patologica

I markers che oggi trovano applicazione stabile e che contribuiscono alla diagnosi istologica di malattia neurodegenerativa vengono valutati:

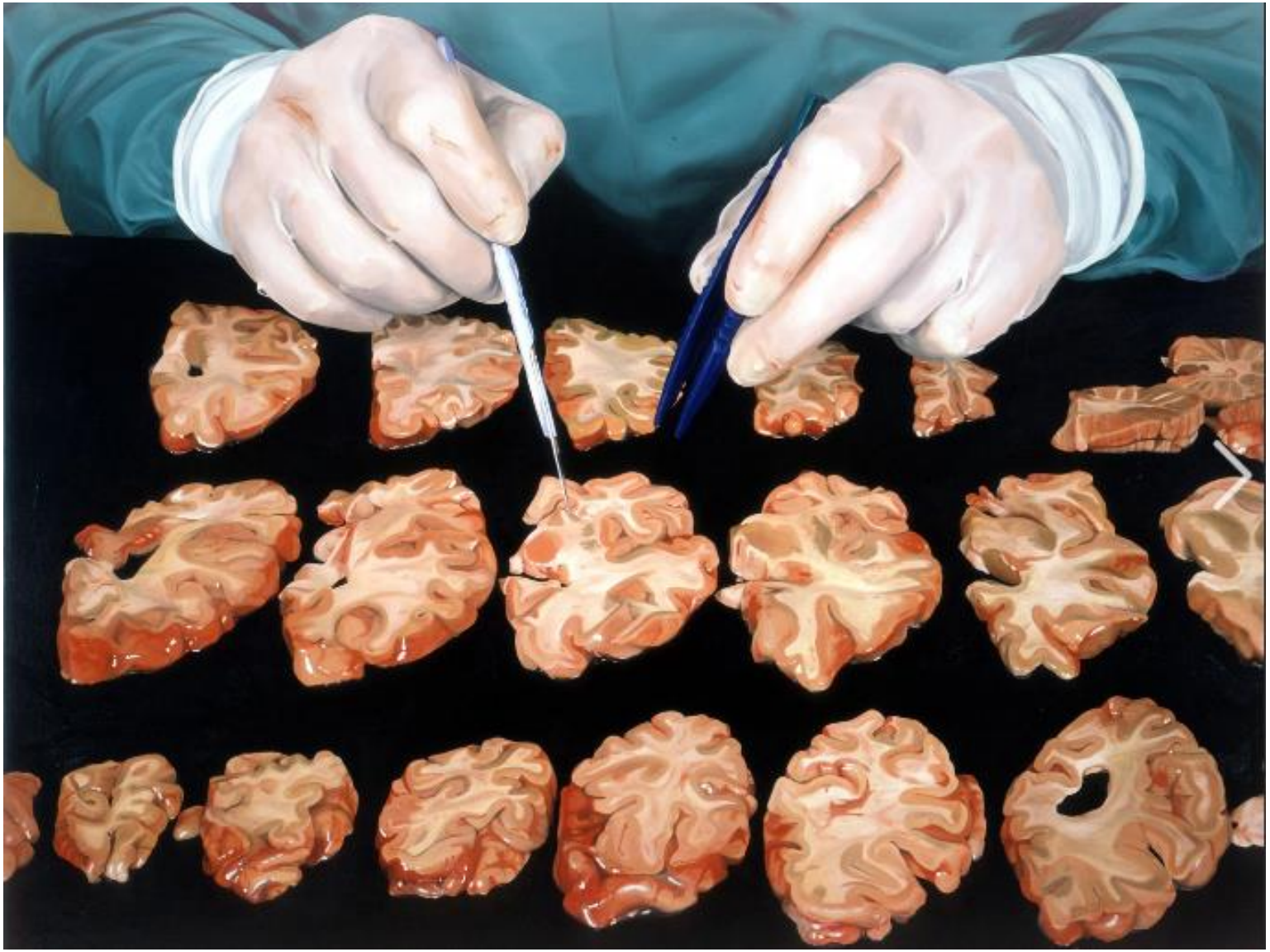
- nella loro distribuzione intracellulare
- nella loro distribuzione topografica

Localizzazione markers istologici-1

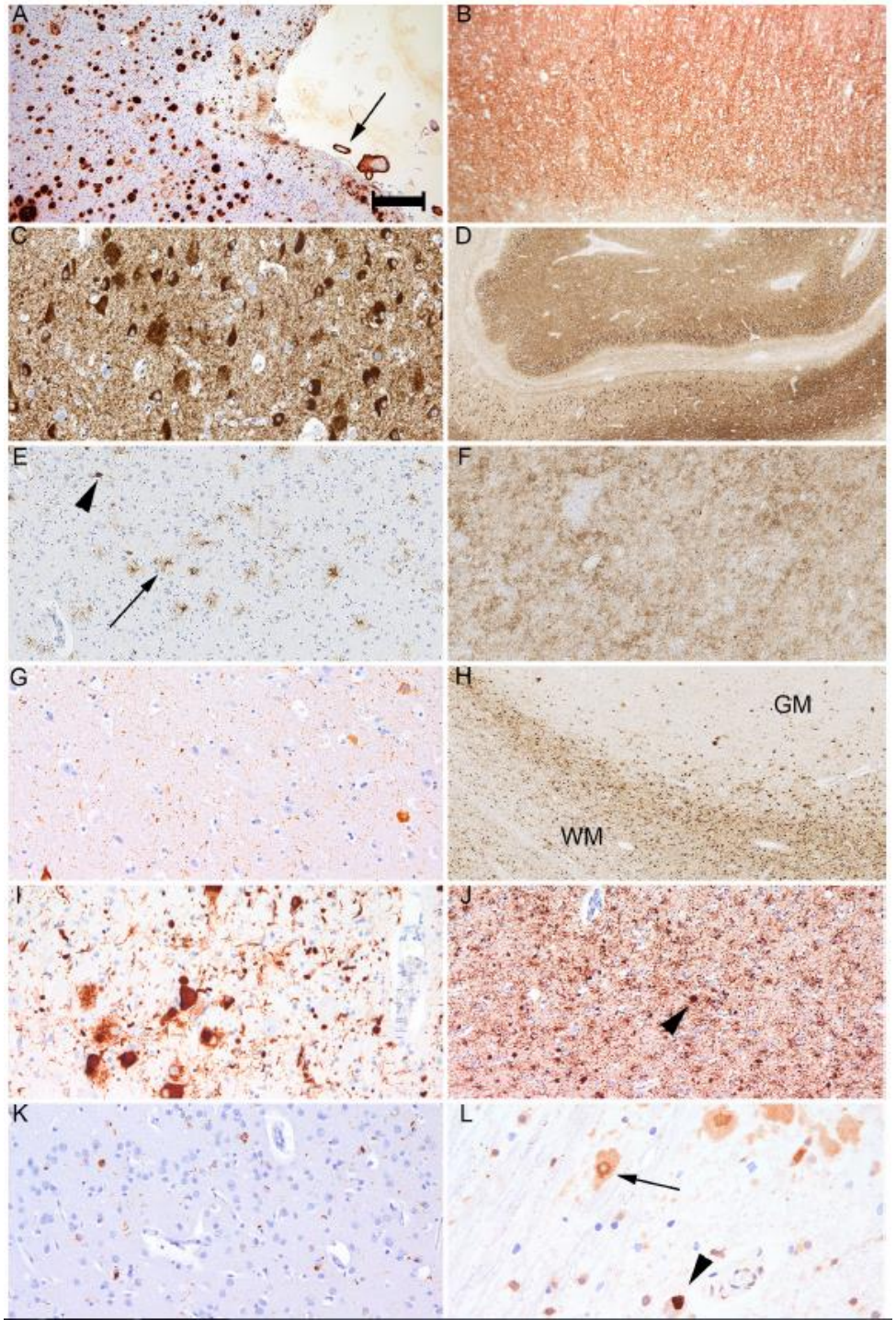


Molecular pathology of neurodegenerative diseases: principles and practice

Kovacs GG. *J Clin Pathol* 2019;**72**:725–735. doi:10.1136/jclinpath-2019-205952



Necessità di sezioni coronali precise su cui standardizzare i prelievi.



Localizzazione markers istologici-2

La nostra esperienza è partita con l'acquisizione di nuovi anticorpi:

- β-amiloide
- α-sinucleina
- Proteina Tau
- TDP 43

Table 1 Stages and phases reported for various tau pathologies and amyloid-beta deposition

Amyloid-beta (AD)[38]	Frontal, parietal, temporal or occipital neocortex.		Phase 1
	Entorhinal region, CA1 and in the insular cortex.		Phase 2
	Basal ganglia, basal forebrain nuclei, thalamus, hypothalamus, white matter.		Phase 3
	Inferior olivary nucleus, the reticular formation of the medulla oblongata, substantia nigra, CA4, central grey of the midbrain, colliculi superiores and inferiores, red nucleus.		Phase 4
	Different nuclei of the pons, cerebellum.		Phase 5
Tau (AD)[45 46 162]	Locus coeruleus, magnocellular nuclei of the basal forebrain.		Stage a–c
	Transentorhinal region.		Stage I
	Entorhinal cortex.		Stage II
	Fusiform and lingual gyri, amygdala, anterior thalamus.		Stage III
	Superior temporal gyrus.		Stage IV
	Frontal, superolateral and occipital (peristriate) regions, striatum.		Stage V
	Secondary and primary neocortical regions and striate area in the occipital lobe, substantia nigra.		Stage VI
Tau (AGD)[107 150]	Ambient gyrus.		Stage 1
	Anterior and posterior medial temporal lobe, temporal pole, subiculum, entorhinal cortex.		Stage 2
	Septum, insular cortex and anterior cingulate gyrus.		Stage 3
	Neocortex and brainstem.		Stage 4
Tau (Pick)[149]	Frontotemporal limbic/paralimbic and neocortical regions.		Phase 1
	Basal ganglia, locus coeruleus and raphe nuclei.		Phase 2
	Primary motor cortex and precerebellar nuclei.		Phase 3
	Visual cortex.		Phase 4
Tau (astro-PSP)[30]	Striatum.		Stage 1
	Frontal-parietal to temporal, to occipital.		Stage 2
	Amygdala.		Stage 3
	Brainstem.		Stage 4
Tau (astro-CBD)[30]	Frontal-parietal.		Stage 1
	Temporal to occipital.		Stage 2
	Striatum and/or amygdala.		Stage 3
	Brainstem.		Stage 4
Tau (GM ARTAG)[30]	Striatum.	Amygdala.	Stage 1
	Cortex or amygdala or brainstem.	Striatum or cortex or brainstem.	Stage 2
	Striatum + amygdala + cortex or striatum + amygdala + brainstem.	Striatum + amygdala + cortex or striatum + amygdala + brainstem or amygdala + cortex + brainstem.	Stage 3
	All regions.	All regions.	Stage 4

AD, Alzheimer's disease; AGD, argyrophilic grain disease; CA, cornu ammonis; CBD, corticobasal degeneration; GM ARTAG, grey matter ageing-related tau astrogliopathy; PSP, progressive supranuclear palsy.

Table 2 Stages, phases and patterns reported for various α-synuclein and TDP-43 pathologies

TDP-43 (bvFTD)[151]	Orbital gyri, gyrus rectus and amygdala.	Pattern I
	Middle frontal and anterior cingulate gyrus, anteromedial temporal lobe areas, superior and medial temporal gyri, striatum, red nucleus, thalamus, precerebellar nuclei.	Pattern II
	Motor cortex, bulbar somatomotor neurons and the spinal cord anterior horn.	Pattern III
	Visual cortex.	Pattern IV
TDP-43 (ALS)[152]	Agranular motor cortex, brainstem motor nuclei of cranial nerves V, VII and X–XII, and spinal cord a-motoneurons.	Stage 1
	Prefrontal neocortex (middle frontal gyrus), brainstem reticular formation, precerebellar nuclei and the red nucleus.	Stage 2
	Prefrontal (gyrus rectus and orbital gyri), and then postcentral neocortex and striatum.	Stage 3
	Anteromedial portions of the temporal lobe, including the hippocampus.	Stage 4
TDP-43 (AD)[154]	Amygdala.	Stage 1
	Entorhinal cortex and subiculum.	Stage 2
	Dentate gyrus of the hippocampus and occipitotemporal cortex.	Stage 3
	Insular cortex, ventral striatum, basal forebrain and inferior temporal cortex.	Stage 4
	Substantia nigra, inferior olive and midbrain tectum.	Stage 5
	Basal ganglia and middle frontal cortex.	Stage 6
aSyn (MSA-P)[156]	Striatum, lentiform nucleus, substantia nigra, brainstem white matter tracts, cerebellar subcortical white matter, motor cortex, mid-frontal cortex and sensory cortex.	Phase 1
	Spinal cord and thalamus.	Phase 2
	Hippocampus and amygdala.	Phase 3
	Visual cortex.	Phase 4
aSyn (MSA-C)[155]	Cerebellum and cerebellar brainstem connectivities.	Phase 1
	Pyramidal and extrapyramidal white matter.	Phase 2
	Neocortex and basal ganglia grey matter.	Phase 3
	Amygdala and hippocampus.	Phase 4
aSyn (Lewy)[72]	Dorsal IX/X motor nucleus and/or intermediate reticular zone (medulla oblongata).	Stage 1
	Caudal raphe nuclei, gigantocellular reticular nucleus, coeruleus–subcoeruleus complex (pons).	Stage 2
	Pars compacta of the substantia nigra (midbrain).	Stage 3
	Temporal mesocortex (transentorhinal region, amygdala) and allocortex (CA2-plexus).	Stage 4
	High-order sensory association areas of the neocortex and prefrontal neocortex.	Stage 5
	First-order sensory association areas of the neocortex and premotor areas, mild changes in primary sensory areas and the primary motor field.	Stage 6

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; C, cerebellar type; CA, Cornu Ammonis; MSA, multiple system atrophy; P, parkinsonian type; TDP-43, Transactive response (TAR) DNAbinding protein 43; aSyn, α-synuclein; bvFTD, behavioural variant of frontotemporal dementia.

Lo studio di tutti gli aspetti di neurodegenerazione e neuroinfiammazione ad essa correlati da parte dell'anatomia patologica non può più essere solo istologico / istochimico / immunoistochimico

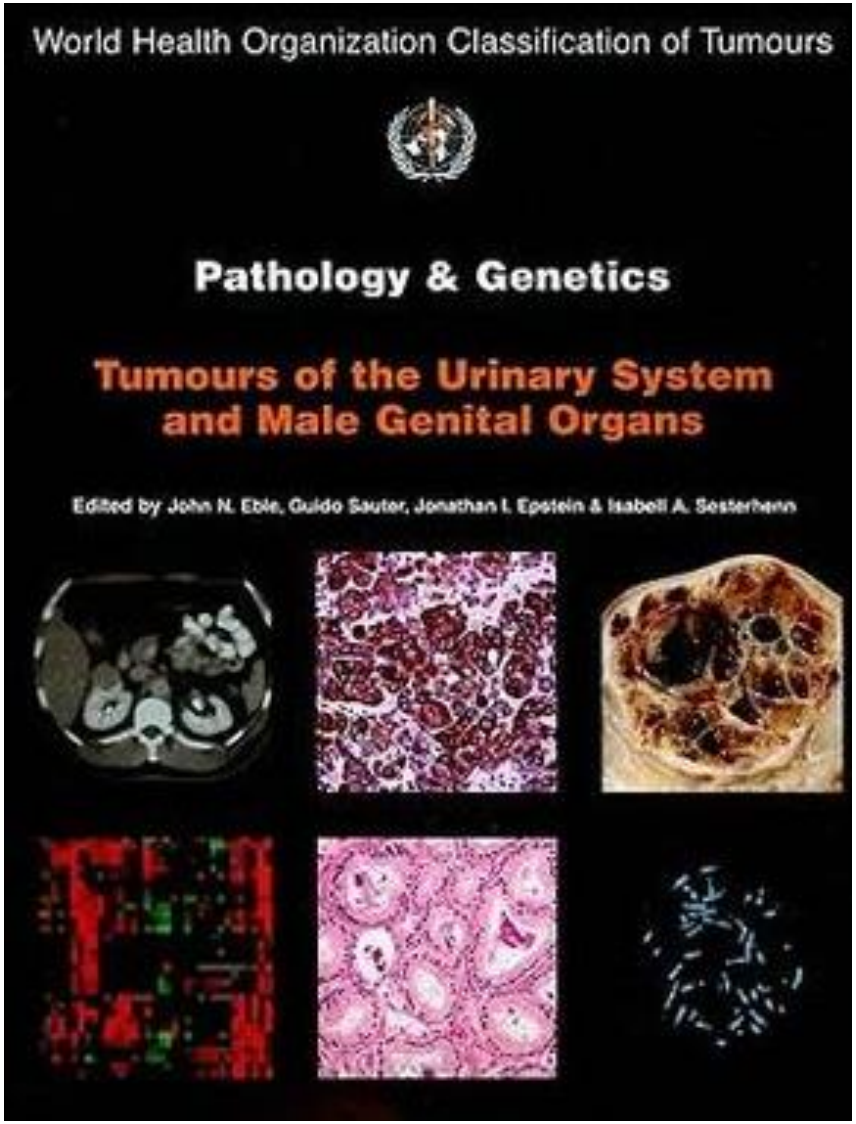
Stretta correlazione molecolare / citogenetica

- Istopatologia
- Molecolare
- Gestione/organizzazione
- Il «passato» nel presente e nel futuro

Tecnologie innovative

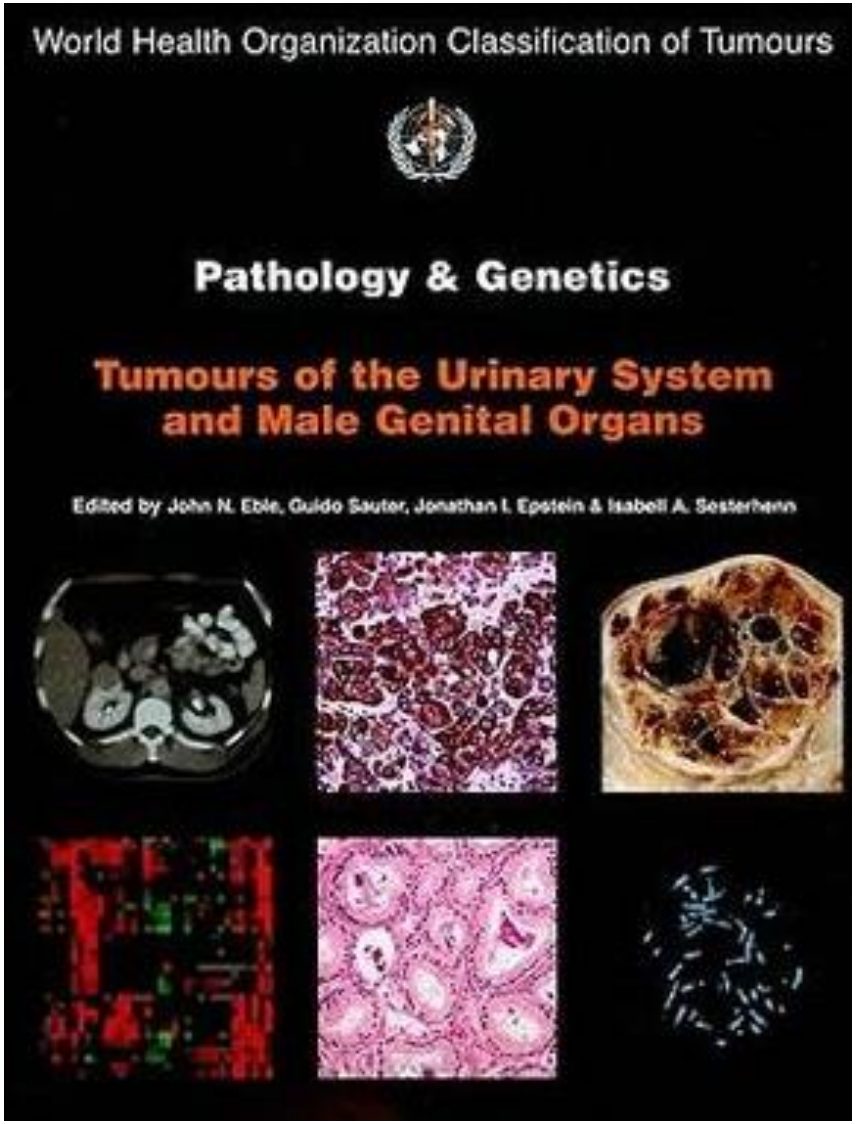
- FISH
  - NGS
    - Nanostring

FISH	NGS	Nanostring
NUCLEO	DNA / RNA	ESPRESSIONE GENICA
Danni cromosomici importanti: • traslocazioni • amplificazioni • delezioni	Sistema ad "alta produttività": • alta sensibilità • molti geni contemporaneamente • molti pazienti contemporaneamente	Soprattutto RNA: • mRNA • miRNA
		Vera e propria conta (senza amplificazione)
		Possibile estensione (anche in contemporanea) a: • DNA • proteine



Tumours of the kidney

- WHO and TNM classifications
- Renal cell carcinoma
- Familial renal cancer
- Clear cell renal cell carcinoma
- Multilocular cystic renal cell
- Papillary renal cell carcinoma
- Chromophobe renal cell carcinoma
- Carcinoma of the collecting ducts of Bellini
- Renal medullary carcinoma
- Renal carcinomas associated with Xp11.2 translocations / TFE3 gene fusions
- Renal cell carcinoma associated with neuroblastoma
- Mucinous tubular spindle cell carcinoma
- Papillary adenoma of the kidney
- Oncocytoma
- Renal cell carcinoma unclassified



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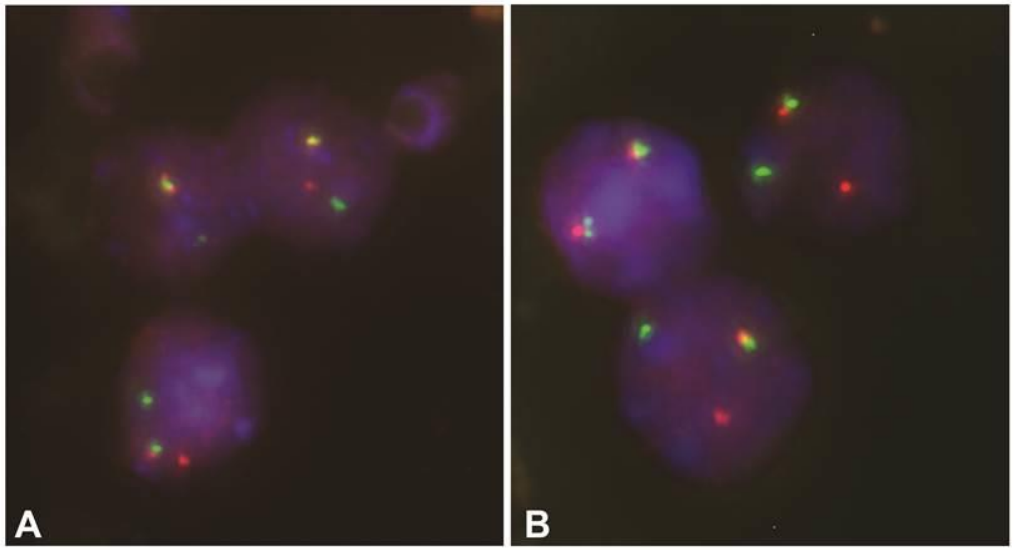
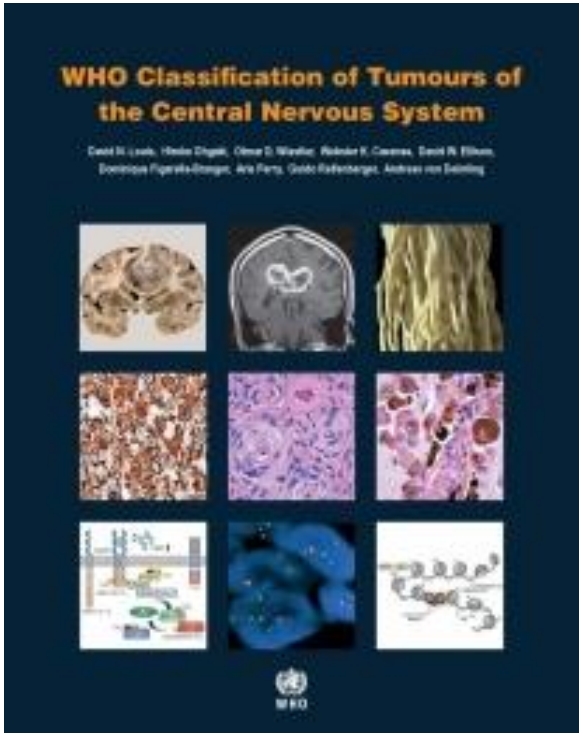
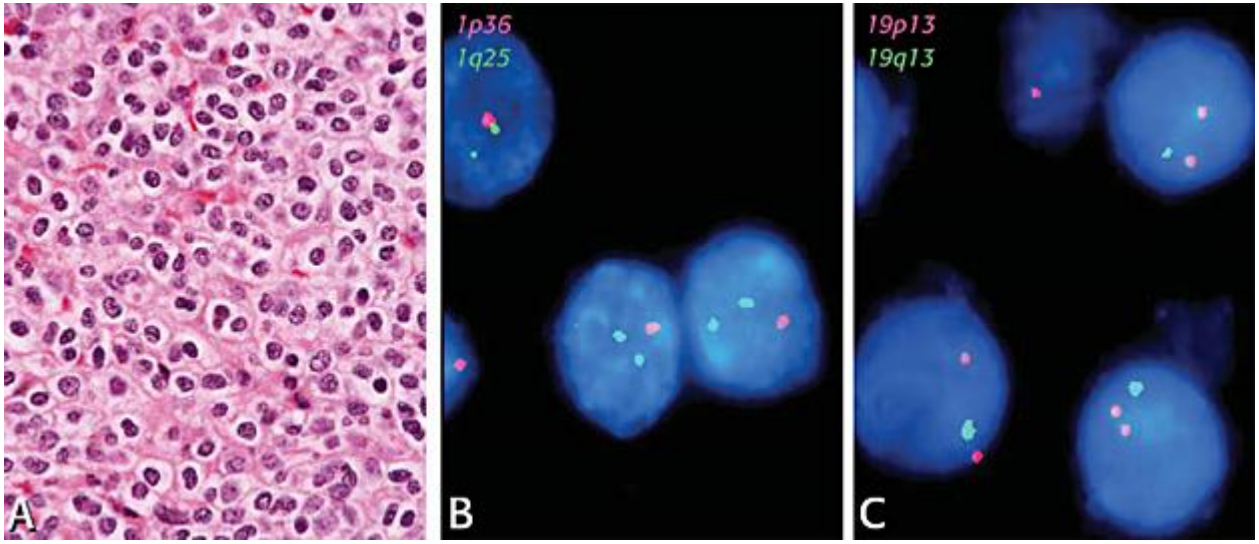


TFEB FISH

Break-apart FISH assay for TFEB-gene rearrangement, similar to that developed for TFE3-gene rearrangement, is now the performed method for confirming the diagnosis of the t(6;11) RCC.

As with the TFE3 FISH assay, one is looking for splitting of the red and green signals, which are normally fused to make a single yellow signal.


WHO Classification of Tumours of the Central Nervous System
WHO


A
1p36
1q25
B
19p13
19q13
C


HiSeqX
illumina
Welcome

FISH	NGS	Nanostring
NUCLEO	DNA / RNA	ESPRESSIONE GENICA
Danni cromosomici importanti: • traslocazioni • amplificazioni • delezioni	Sistema ad ‘’alta produttività’’: • alta sensibilità • molti geni contemporaneamente • molti pazienti contemporaneamente	Soprattutto RNA: • mRNA • miRNA
		Vera e propria conta (senza amplificazione)
		Possibile estensione (anche in contemporanea) a: • DNA • proteine

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An Overview of Next Generation Sequencing and its Application in Neurodegenerative Diseases

Kritika Sehgal, Stuti Agarwal, Aarushi Tandon, Avantika Mishra, *Chakresh Kumar Jain,
Department of Biotechnology

frontiers in
CELLULAR NEUROSCIENCE

HYPOTHESIS AND THEORY ARTICLE
published: 27 March 2014
doi: 10.3389/fncel.2014.00089

Emerging bioinformatics approaches for analysis of NGS-derived coding and non-coding RNAs in neurodegenerative diseases

Alessandro Guffanti[1,2]*, Alon Simchovitz[1] and Hermona Soreq[1]*

[1] *Laboratory of Molecular Neuroscience, Department of Biological Chemistry, The Edmond and Lily Safra Center of Brain Science, The Hebrew University of Jerusalem, Jerusalem, Israel*
[2] *Bioinformatics, Genomnia srl, Milano, Italy*

FISH	NGS	Nanostring
NUCLEO	DNA / RNA	ESPRESSIONE GENICA
Danni cromosomici importanti: • traslocazioni • amplificazioni • delezioni	Sistema ad ‘’alta produttività’’: • alta sensibilità • molti geni contemporaneamente • molti pazienti contemporaneamente	Soprattutto RNA: • mRNA • miRNA
		Vera e propria conta (senza amplificazione)
		Possibile estensione (anche in contemporanea) a: • DNA • proteine

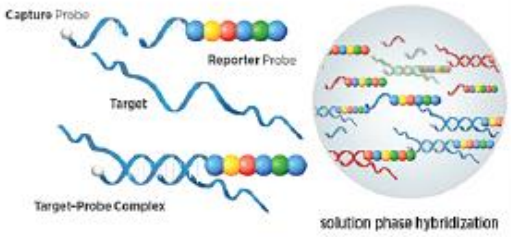
Nanostring

NanoString's nCounter Analysis System performs a highly multiplexed, digital quantification of up to 800 genes in a single reaction. This is achieved with the help of reporter codesets, which are color-coded "barcodes" specific for each gene.

Workflow consists of three major steps:

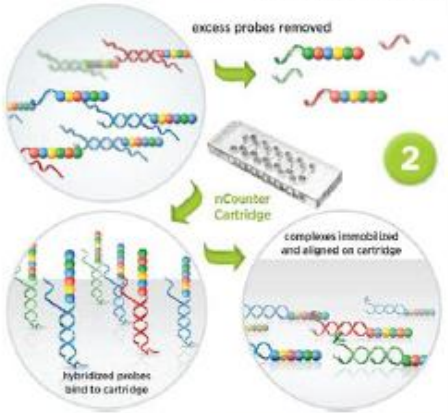
1 Hybridization

In the hybridization step, sample material is mixed with excess codeset and the codeset hybridizes to the mRNA target in solution.



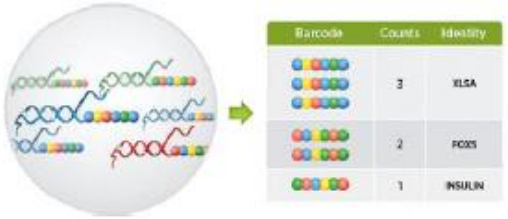
Purification

Purification is carried out robotically which removes excess codeset and immobilizes the codeset/RNA complexes in the nCounter cartridge for data collection.



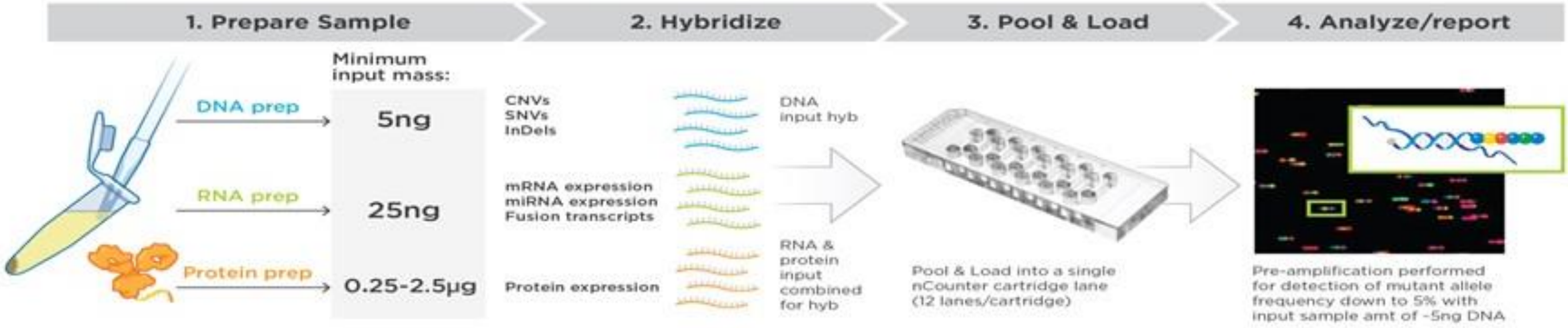
3 Digital imaging

CCD capture technology is used for data collection and digital images are processed and reporter probe counts are tabulated for data analysis using NanoStrings nSolver analysis software and advanced analysis modules.

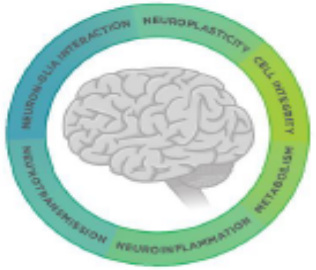


Nanostring technology

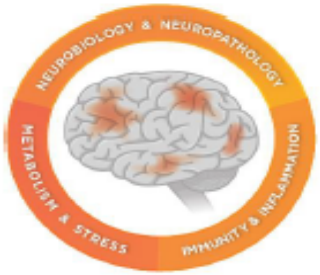
- The nCounter Analysis System utilizes a novel digital barcode technology for direct multiplexed measurement of analytes
- The technology uses molecular "barcodes" and single molecule imaging for the direct hybridization and detection of hundreds of unique transcripts in a single reaction
- No enzymes or library prep required to perform assay



nCounter Neuropathology Panel



nCounter Neuroinflammation Panel

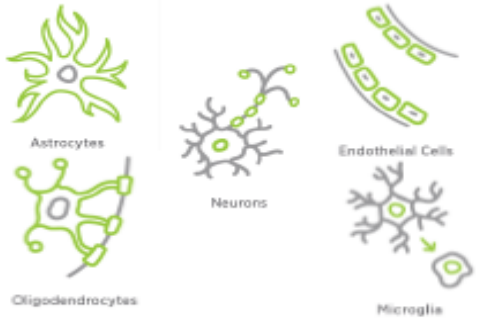


Human & Mouse Panels
770 Genes

>20 Pathways

Cell Type Profiling

CNS-specific Cell Type Profiling



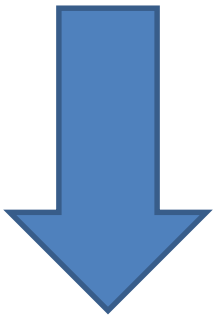
Peripheral Immune Cell Profiling

B-cells	Mast cells
CD45+ cells	Neutrophils
CD8 T cells	NK CD56dim cells
Cytotoxic cells	NK cells
Dendritic cells	T-cells
Exhausted CD8	T_H1 cells
Macrophages	T_{reg}

Axon and Dendrite Structure	Compartmentalization & Structural Integrity	Adaptive Immune Response	Immunity & Inflammation
Neural Connectivity		Cytokine Signaling	
Neuronal Cytoskeleton		Inflammatory Signaling	
Tissue Integrity		Innate Immune Response	
Autophagy	Metabolism	Microglia Function	
Carbohydrate Metabolism		NF-kB	
Lipid Metabolism		Autophagy	Metabolism & Stress
Oxidative Stress		Carbohydrate Metabolism	
Transcription and Splicing		Cellular Stress	
Unfolded Protein Response		Lipid Metabolism	
Activated Microglia	Neuroinflammation	Angiogenesis	Neurobiology & Neuropathology
Cytokines		Apoptosis	
Matrix Remodeling		Astrocyte Function	
Myelination	Neuron-Glia interaction	Cell Cycle	
Trophic Factors		DNA Damage	
Angiogenesis	Neuroplasticity, Development & Aging	Epigenetic Regulation	
Apoptosis		Growth Factor Signaling	
Chromatin Modification		Insulin Signaling	
Growth Factor Signaling		Matrix Remodeling	
Transmitter Release	Neurotransmission	Neurons and Neurotransmission	
Transmitter Response and Reuptake		Notch	
Transmitter Synthesis and Storage		Oligodendrocyte Function	
Vesicle Trafficking		Wnt	

Obiettivo

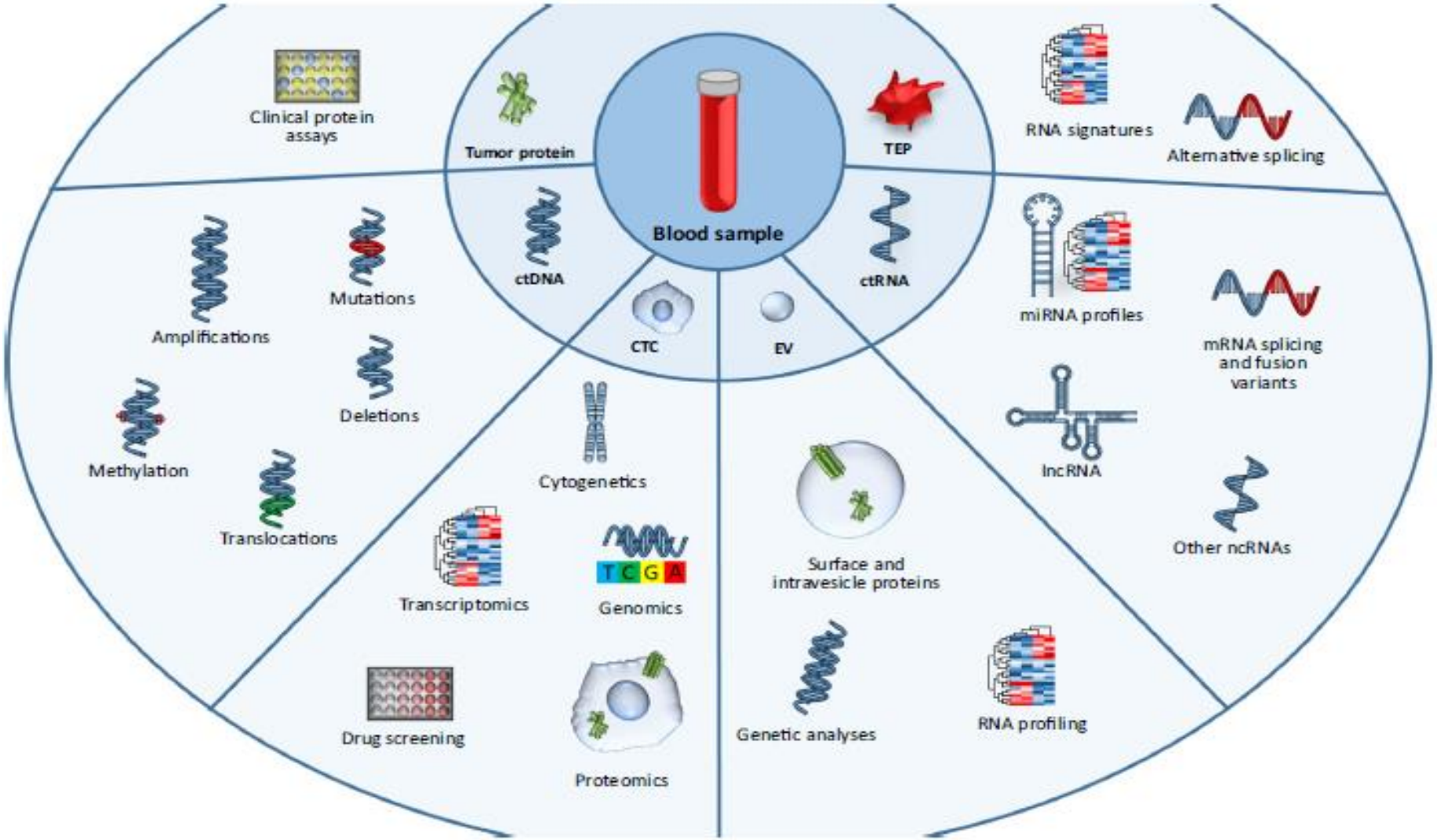
Poter trovare serie di alterazioni da raggruppare in chip non troppo ampi



Possibile approccio su biopsia liquida

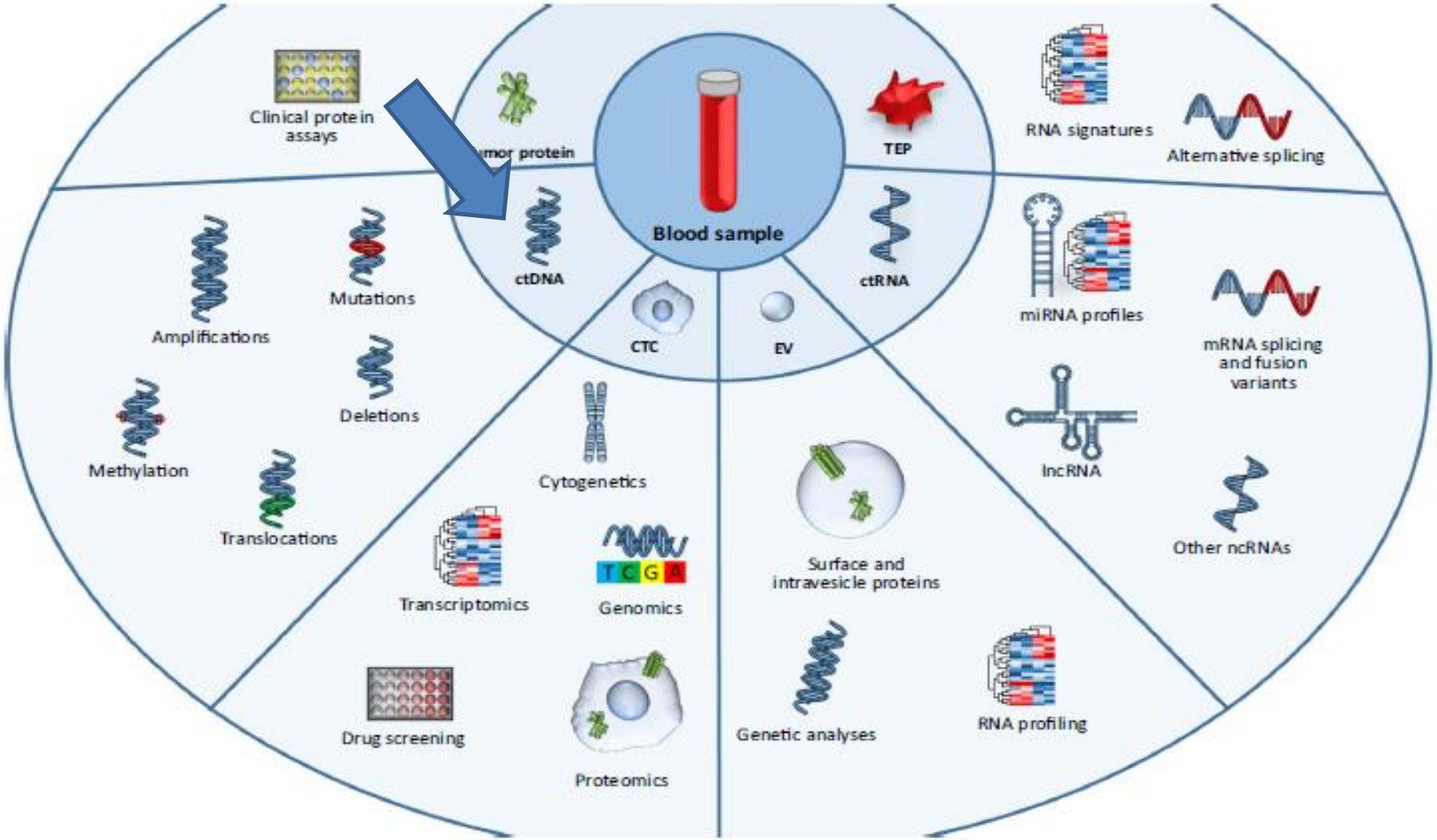
Key Figure

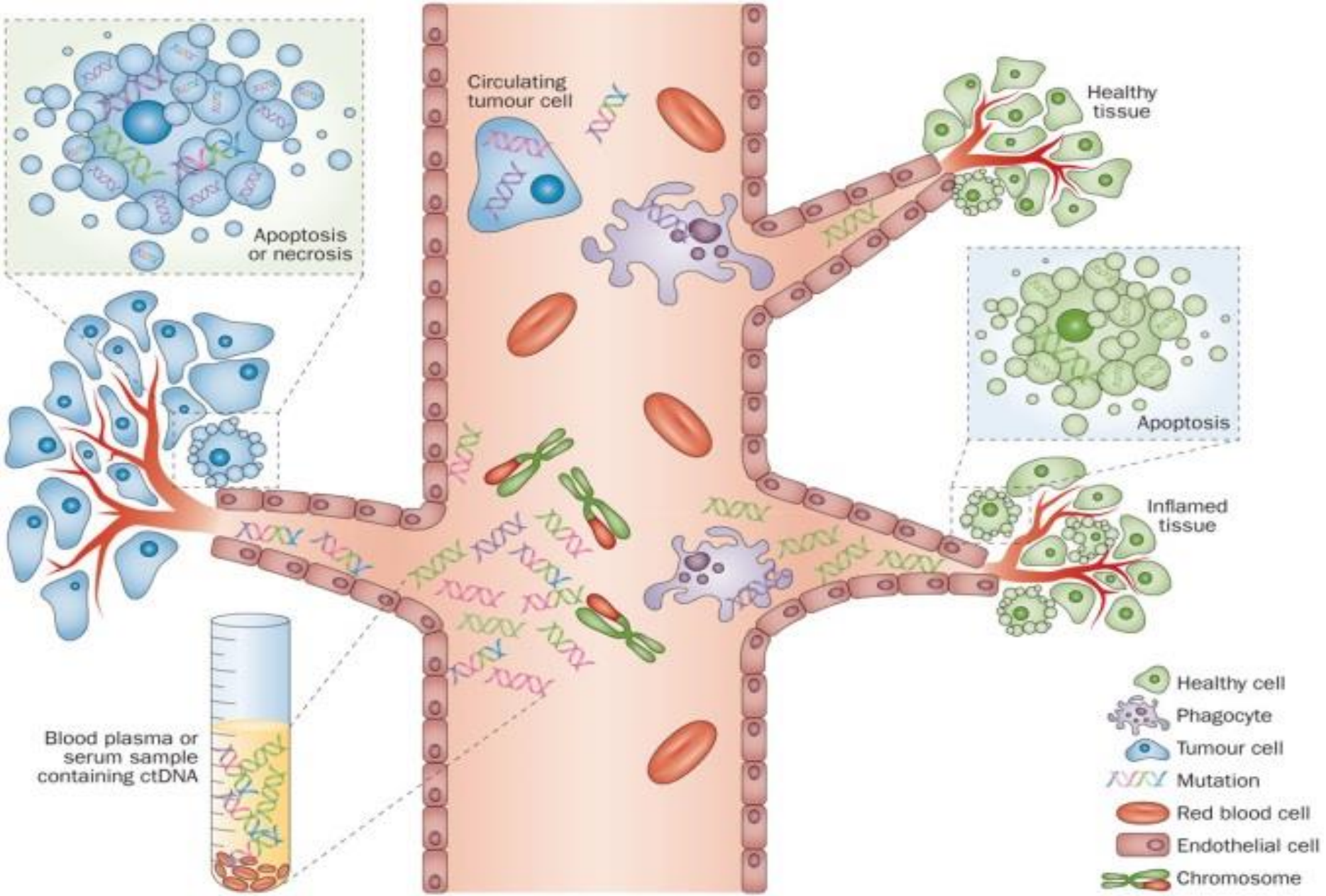
Components of the Tumor Circulome



Key Figure

Components of the Tumor Circulome




Apoptosis or necrosis
Circulating tumour cell
Healthy tissue
Apoptosis
Inflamed tissue
Blood plasma or serum sample containing ctDNA
Healthy cell
Phagocyte
Tumour cell
Mutation
Red blood cell
Endothelial cell
Chromosome

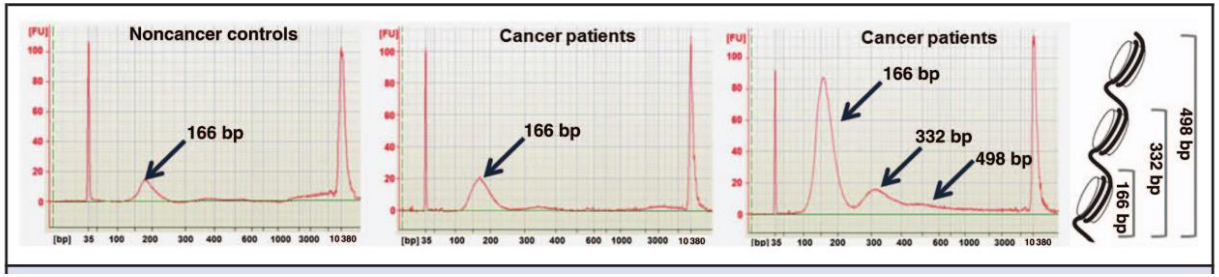
Meccanismo di rilascio del ctDNA

- **Secrezione attiva**

  acidi nucleici rilasciati dalle cellule tumorali

- **Rilascio passivo**

  dalle cellule tumorali necrotiche e apoptotiche



- ctDNA certamente rappresenta **la componente del "circuloma" maggiormente studiata** nella pratica clinica della biopsia liquida

- ctDNA costituisce il solo tipo di campione che è stato **ufficialmente approvato** per uso clinico nei pazienti con NSCLC

ORGANI PERIFERICI

Alcune delle proteine associate alla neurodegenerazione possono essere trovate negli organi periferici

Acta Neuropathol (2010) 120:1–12
DOI 10.1007/s00401-010-0706-x

REVIEW

Involvement of the peripheral nervous system in synucleinopathies, tauopathies and other neurodegenerative proteinopathies of the brain

Koichi Wakabayashi · Fumiaki Mori · Kunikazu Tanji · Satoshi Orimo · Hitoshi Takahashi

Cell and Tissue Research (2018) 373:267–286
https://doi.org/10.1007/s00441-018-2851-9

REVIEW

Peripheral and central autonomic nervous system: does the sympathetic or parasympathetic nervous system bear the brunt of the pathology during the course of sporadic PD?

Satoshi Orimo[1] · Estifanos Ghebremedhin[2] · Ellen Gelpi[3,4]

Neuroscience Letters 696 (2019) 132–139

Contents lists available at ScienceDirect

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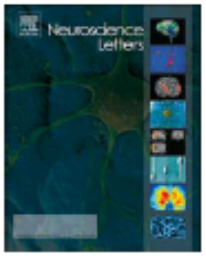
journal homepage: www.elsevier.com/locate/neulet



Research article

Tau immunoreactivity in peripheral tissues of human aging and select tauopathies

Brittany N. Dugger[a,*], Brittany R. Hoffman[b], Alex Scroggins[b], Geidy E. Serrano[b], Charles H. Adler[c], Holly A. Shill[d], Christine M. Belden[b], Marwan N. Sabbagh[d,e], John N. Caviness[c], Erika Driver Dunckley[c], Thomas G. Beach[b]

[a] Department of Pathology and Laboratory Medicine University of California, Davis, Sacramento, CA, United States
[b] Banner Sun Health Research Institute, Sun City, AZ, United States
[c] Parkinson's Disease and Movement Disorders Center, Department of Neurology, Mayo Clinic, Scottsdale, AZ, United States
[d] Barrow Neurological Institute, Phoenix, AZ, United States
[e] Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV, United States

Key Figure

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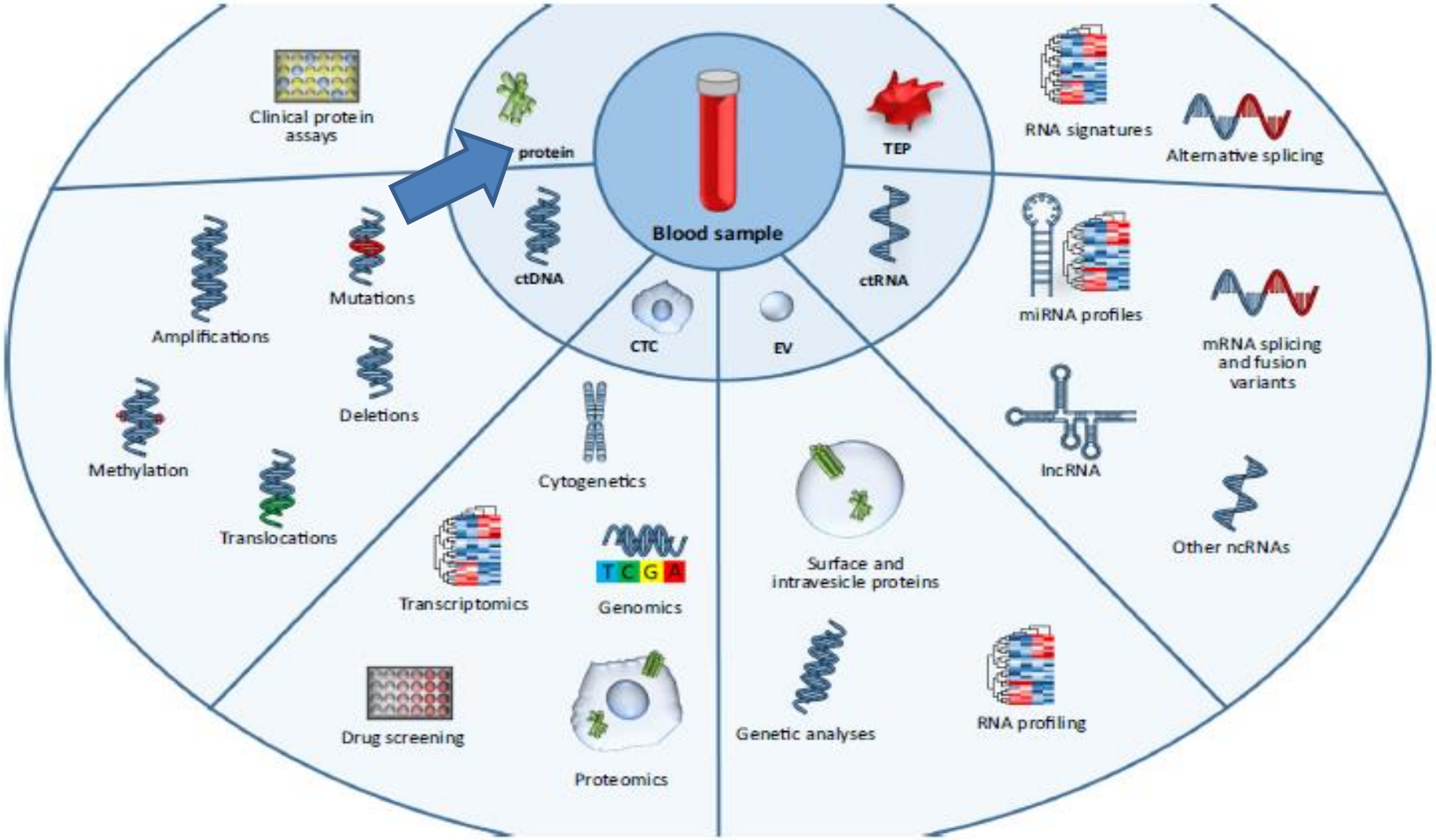


- Istopatologia
- Molecolare
- Gestione/organizzazione
- Il «passato» nel presente e nel futuro

Goals

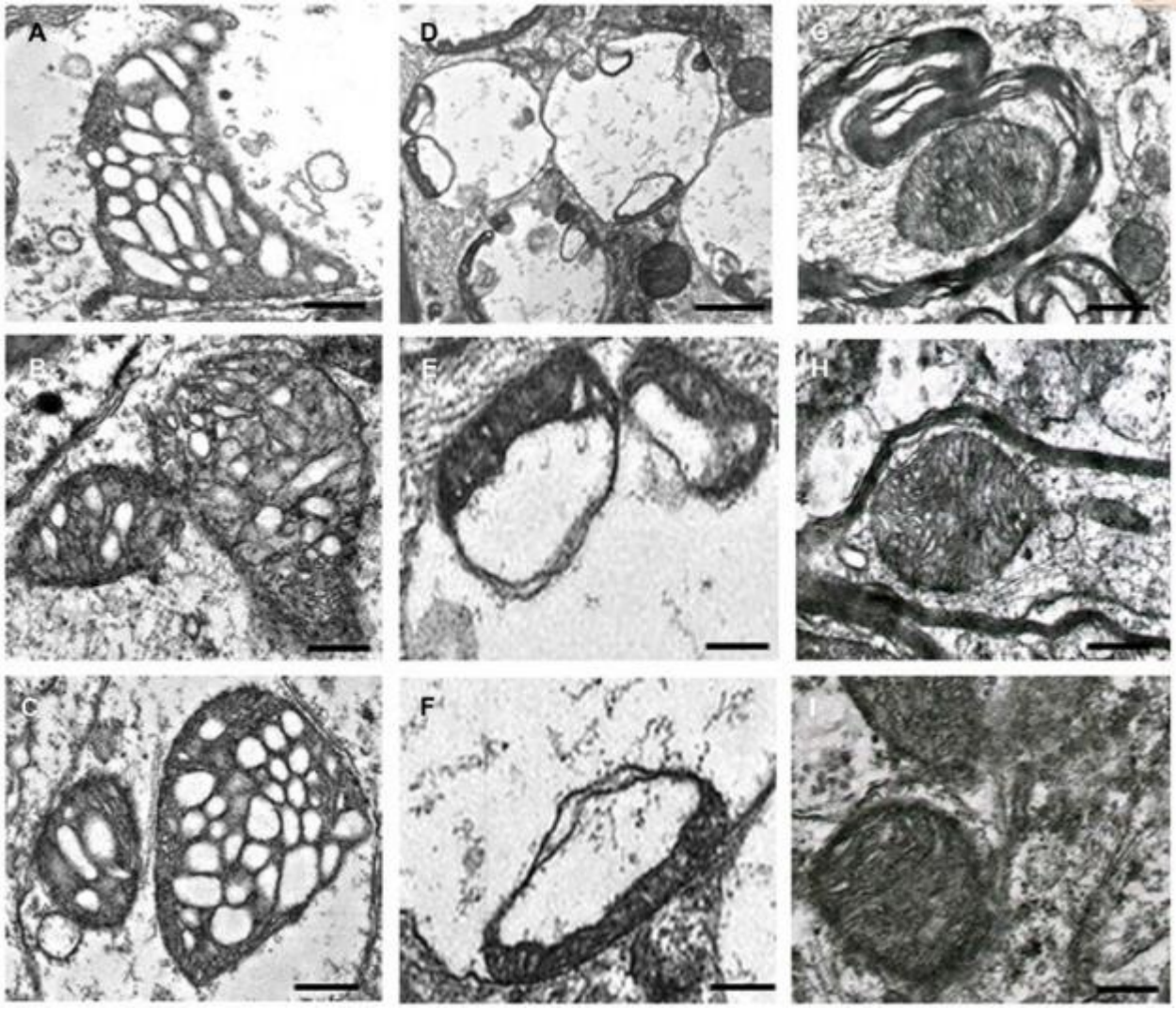
- Centralizzazione dei dati (clinici, strumentali, psicologici, bioumorali)
- Unico database
- Creazione di un modello
- Collaborazione
- Autopsie condivise
- Studio della genesi infiammatoria di queste patologie

Ampliamenteo di conoscenze e casistica con centri di riferimento:

- nazionali
- internazionali

- Istopatologia
- Molecolare
- Gestione/organizzazione
- Il «passato» nel presente e nel futuro

Lou Gehrig, 1903-1941



Paradigm of severe mitochondrial alterations in ALS motor neurons. The first **(A–C)** and the second column **(D–F)** show at low and high magnification, respectively, the severe damage produced to mitochondria by the SOD1 G93A ALS-inducing mutation. On the right column **(G–I)**, the beneficial effects of autophagy, induced by lithium, are evident. Scale bars: **A–C** = 0.12 μm; **D** = 0.55 μm; **E** = 0.15 μm; **F** = 0.13 μm; **G–I** = 0.12 μm; from Fornai et al. (2008a), Supporting Information, SI Figure 21; Copyright (2008) National Academy of Sciences, USA.

Niemann-Pick

La malattia fu descritta per la prima volta da Albert Niemann nel 1914 in un bambino con epato-spleno megalia, linfoadenopatia e deterioramento neurologico progressive, che morì all'età di 2 anni.

Lo studio istopatologico fu poi condotto da Ludvig pick che dimostrò la presenza di cellule schiumose simili, ma non identiche, a quelle trovate nella malattia di Gaucher.

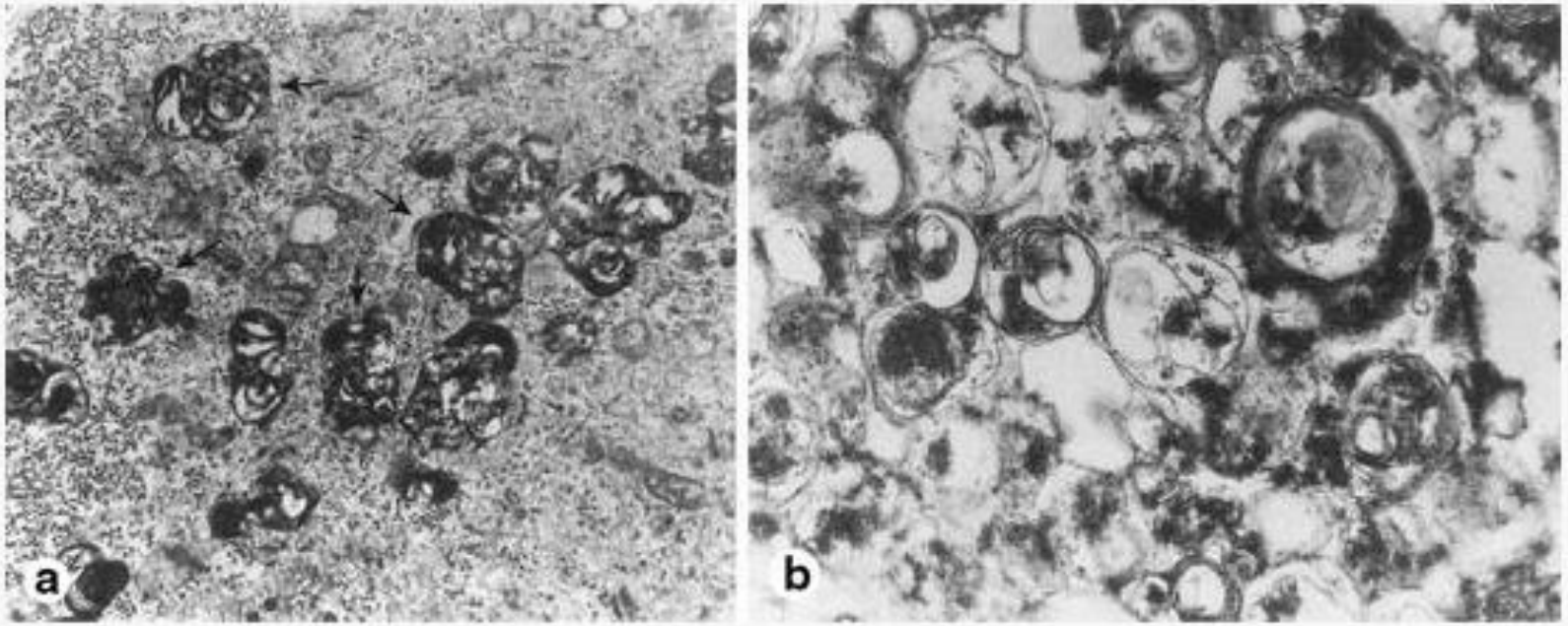


Fig. 34.5

Niemann–Pick disease electron micrographs (**a**) Pleomorphic lipid profiles in the liver. (**b**) Cultured fibroblast with pleomorphic lipid profiles (From Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Elsevier; 2007, with permission)

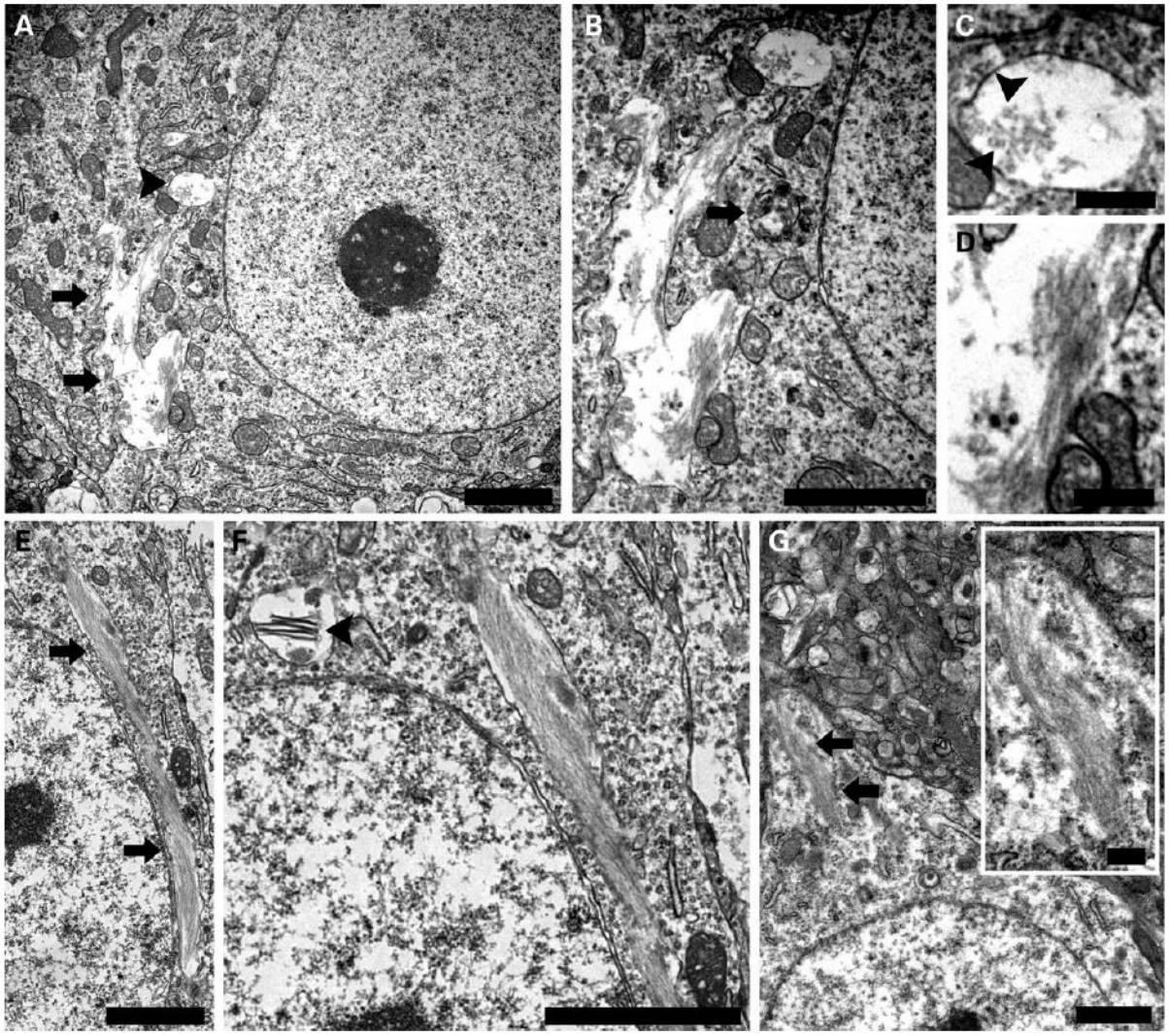


Figure 7. Ultrastructure of GlcCer storage in nGD neurons. Neurons were from the cerebral cortex of −/− mice at 14 (**A**–**F**) and 21 (**G**) days of age. (A–D) A prominent vacuolar inclusion (arrows in A) in the perikaryoplasm of a large neuron to the left of the nucleus, containing dilute arrays of fibrils and pseudotubules, most of which are longitudinal but sometimes transverse as in the upper vacuole (arrowhead in A), which is probably a continuation of the same membrane-bound compartment indicated by the arrows. (B–D) Higher magnifications of the inclusions so as to resolve the encompassing membrane and the tubular appearance of its contents (C and D) seen in cross-section in (C) (arrowheads). An unrelated inclusion body (arrow) is also present in (B). (**E** and **F**) A large neuron with an inclusion body (arrows) (~9 μm in length) showing more densely packed pseudotubules. A rounded vacuole in (F) includes dense fibrils (arrowhead) that might correspond to flattened GlcCer bilayer stacks (32). (**G**) A neuron with pseudotubules (arrows) running into a process which is not clearly membrane-delimited (further magnified in the inset). Scale bars are all 2 μm except for (**C**) and (**D**) which are 0.5 μm.

La disfunzione del Sistema endosomale/lisosomiale è comune a molte condizioni neurodegenerative

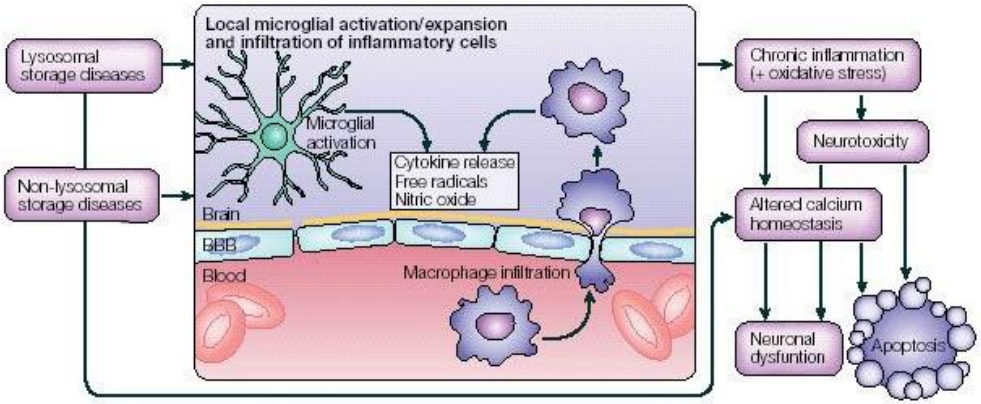
- Alzheimer
- Parkinson
- Demenza fronto-temporale
- Malattia di Alexander
- Malattie del muscolo scheletrico

Review Article | Published: 27 July 2005

Storage solutions: treating lysosomal disorders of the brain

nature reviews neuroscience

Mylvaganam Jeyakumar, Raymond A. Dwek, Terry D. Butters & Frances M. Platt



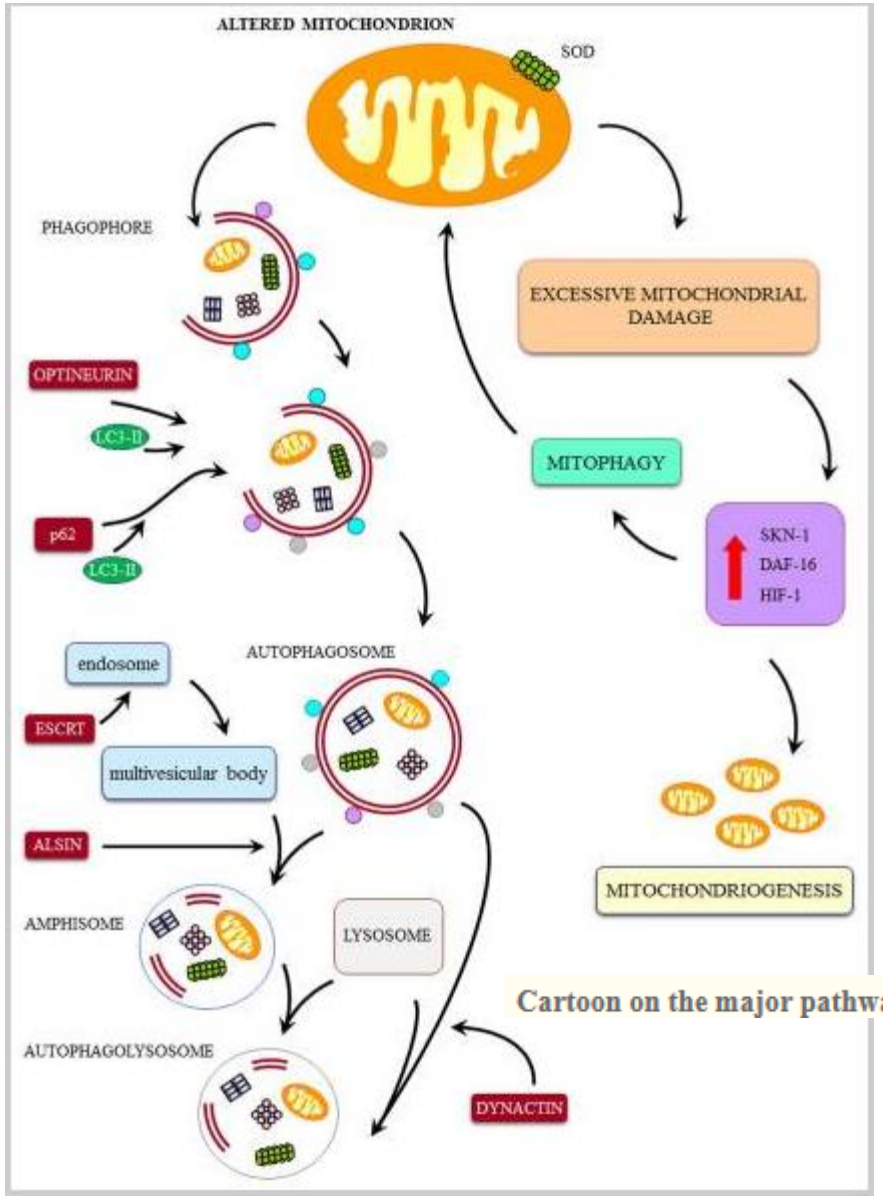
Chronic microglial activation and macrophage infiltration are prominent features in the CNS of patients and mouse models with the gangliosidoses and non-lysosomal storage disorders — namely, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease and prion diseases (see also Box 3). Activated resident microglial cells and recruited macrophages that cross the blood–brain barrier (BBB) generate oxygen-free radicals, nitric oxide and other potentially toxic products, such as cytokines. This leads to chronic inflammation, which is accompanied by oxidative stress — a process that parallels disease progression in animal models of both lysosomal storage disorders and more common neurodegenerative diseases. Although these diseases have distinct pathogenic causes that lead to microglial activation, the mechanisms that contribute to neurodegenerative processes, such as neuronal dysfunction and apoptosis, are not exclusive to each disorder; for example, altered calcium homeostasis is another common feature of many lysosomal storage disorders and more common neurodegenerative diseases.

Ultrastructural studies of ALS mitochondria connect altered function and permeability with defects of mitophagy and mitochondriogenesis

Riccardo Ruffoli,[1] Alessia Bartalucci,[1] Alessandro Frati,[2] and Francesco Fornai[1,2,*]

frontiers in Cellular Neuroscien

Front Cell Neurosci. 2015; 9: 341.



Cartoon on the major pathways involved in mitochondrial integrity and a few examples of ALS-related

IL CERVELLO CHE CAMBIA 9

Review

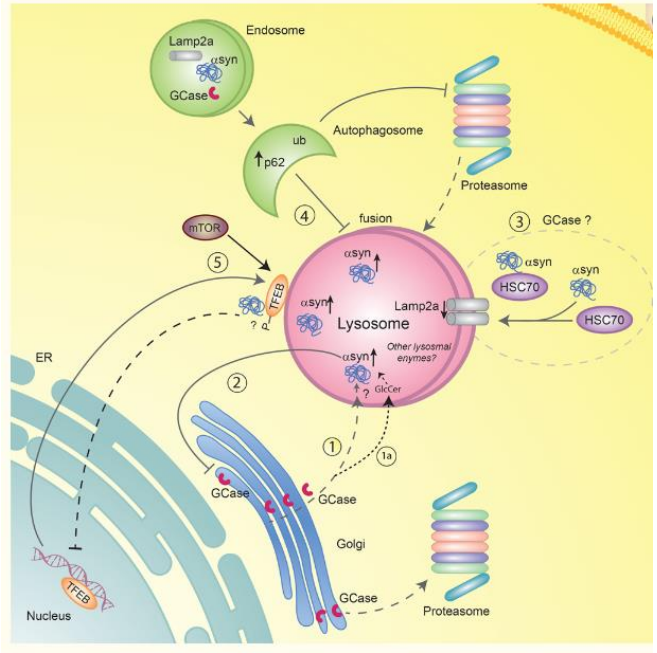
The lysosomal storage disease continuum with ageing-related neurodegenerative disease

Lloyd-Evans, E., & Haslett, L. J. (2016).

The complicated relationship between Gaucher disease and Parkinsonism: Insights from a rare disease

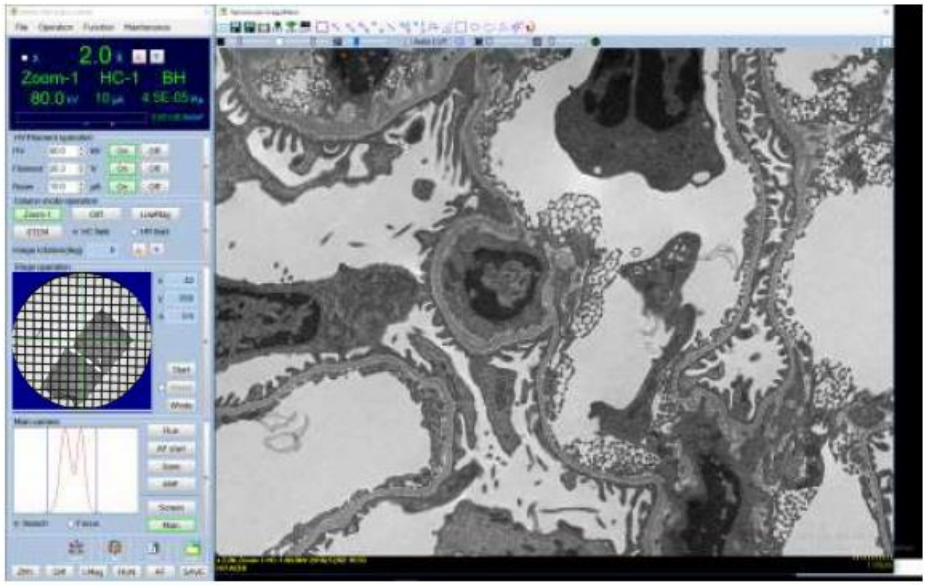
Elma Aflaki, Wendy Westbroek, and Ellen Sidransky*

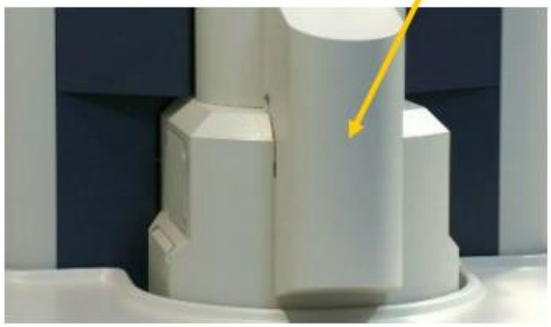
Neuron. 2017 Feb 22; 93(4): 737–746.

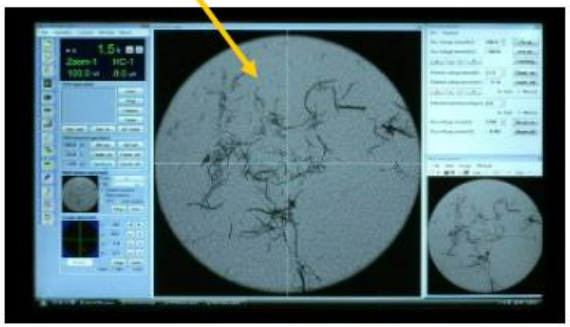


Pathways that might contribute to the association between GD and PD

Fully digitized HITACHI Transmission Electron Microscope Model HT7800 with 120kV including W- and LaB6- Cathode







Simple operation via the Hitachi Button Panel for TEM and STEM applications


5
6
7
8

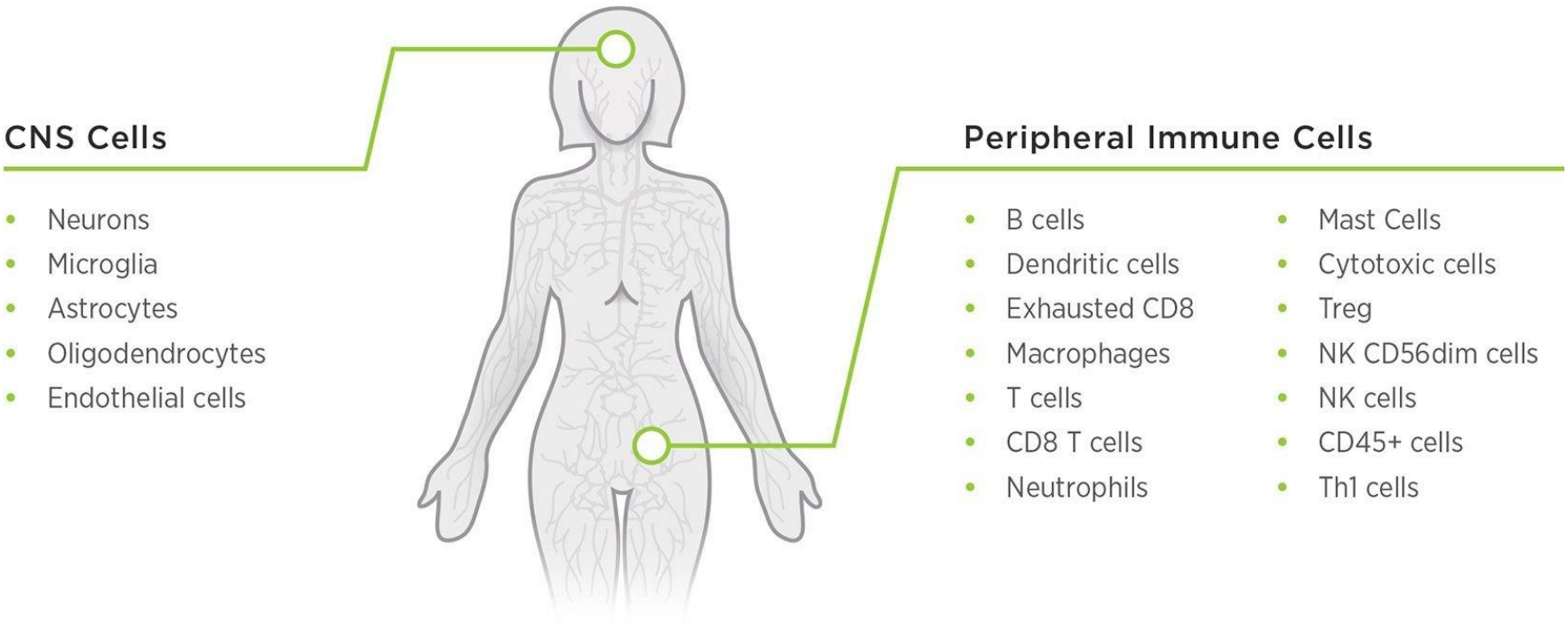
GRAZIE!

- Prof. Ravetti
- UOS Diagnostica Molecolare (Dott.ssa S.Zupo)
- Dott.ssa S.Salvi

UOS Diagnostica Molecolare

OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria

SNC e Profilo cellulare immunologico periferico



- **Neuroinflammation Panel Functional Annotations**
- Functional annotations for 23 pathways and processes were assigned across the genes in the Neuroinflammation Panels. The 23 pathways and processes represent three core themes of neuroinflammation: immunity and inflammation, neurobiology and neuropathology, and metabolism and stress.
- **Immunity and Inflammation**
- The role of innate immunity in many neurological disorders is now widely accepted in the research world although the relative contributions of these processes to the progression and/or amelioration of these diseases is incompletely understood. Several key processes and pathways are assessed in this panel to provide a comprehensive view of the immune and inflammatory response in the nervous system.

Neurobiology and Neuropathology

Neuropathology research today requires a broad view of all the underlying aspects of neurological disorders and injury, including assessment of neurotransmission, neuron-glia interactions, neuroplasticity, cell integrity, neuroinflammation, and metabolism.

There are 13 pathways and processes included in this panel to evaluate the impact of neuroinflammation and immune actions in the nervous system on neuropathology.

Metabolism and Stress

Metabolic dysfunction and stress have been shown to influence brain activity and disrupt CNS homeostasis and cognitive function by adopting neurotoxic functions.

The genes selected for this panel are designed to assess important aspects of metabolism and stress that are known to impact neuroinflammation.

Review article

Pitfalls in molecular diagnostics

Seminars in Diagnostic Pathology 36 (2019) 342–354

Lulu Sun, John D. Pfeifer*

Pathology and Immunology Department, Washington University School of Medicine, 660 S. Euclid Ave., Box 8118, St. Louis, MO 63110, United States

Cartoon on the major pathways involved in mitochondrial integrity and a few examples of ALS-related alterations. The mitochondrial dysfunctions in ALS may be produced by a direct mitochondrial toxicity (exemplified here by SOD1-induced mitochondrial toxicity) or a defect in the removal of altered mitochondria by the autophagy/mitophagy pathway. These include: (1) defect in the merging of autophagosome with lysosome (dynactin mutation); (2) defect of merging of endosome with autophagosome to produce amphisome (alsin mutation); (3) defect in linking ubiquitinated protein aggregates to the autophagy machinery by the autophagy protein p62 (SQSTM1 mutation); (4) defect of the fusion of autophagosomes with endosomes and lysosomes (CHMP2B mutation); (5) defect in vesicles trafficking beyond the autophagosome (dynactin mutation); (6) defect in parkin-mediated mitophagy (Optineurin mutation); (7) defect in autophagosome maturation and mitophagy (VCP mutation); and (8) defect in trafficking of autophagy compartments (C9orf72 mutation). Despite a sole defect in the biogenesis of mitochondria may potentially lead to accumulation of degenerated mitochondria, to our knowledge a specific familial ALS (fALS) phenotype due to such a defect was not described so far. Nonetheless, it is likely that, due to a dual tightened control of mitochondrial removal and biogenesis of mitochondria, a failure in the first pathway will eventually lead to a failure in the biogenesis of novel mitochondria. Thus, it is not surprising that, in all fALS phenotypes featuring a defect in the progression of autophagy, we can detect only giant, altered mitochondria in the absence of small, newly synthesized mitochondria. This confirms the eventual concomitance of mitophagy and mitochondriogenesis as indicated by Palikaras et al. (2015a,b). Degenerated mitochondria, to our knowledge a specific fALS phenotype due to such a defect was not described so far. Nonetheless, it is likely that, due to a dual tightened control of mitochondrial removal and biogenesis of mitochondria, a failure in the first pathway will eventually lead to a failure in the biogenesis of novel mitochondria. Thus, it is not surprising that, in all fALS phenotypes featuring a defect in the progression of autophagy, we can detect only giant, altered mitochondria in the absence of small, newly synthesized mitochondria. This confirms the eventual concomitance of mitophagy and mitochondriogenesis as indicated by Palikaras et al. (2015a,b).

PROTEINE MULTIPLE

La presenza concomitante di proteine associate alla neurodegenerazione è frequente.

PROTEINE

La maggior parte di queste proteine segue un pattern di distribuzione sequenziale nell'encefalo.

IPOTESI

Proposto un meccanismo di «insemenzamento» / propagazione «cellula per cellula»

Pathways that might contribute to the association between GD and PD

Pathways that might contribute to the association between GD and PD

Wild-type GCase is produced in the ER, glycosylated in the Golgi and is translocated to the lysosome where it degrades its substrate, GlcCer. **(1)** Mutant GCase may undergo proteosomal breakdown, is not translocated to lysosomes. **(1a)** GlcCer accumulates in the lysosome, which subsequently may lead to α-syn aggregation; however, not all individuals carrying a mutation develop PD. **(2)** In PD, the oligomeric form of α-syn may suppress ER-Golgi trafficking of GCase which can result in reduced GCase activity. **(3)** α-syn is a substrate for a selective form of autophagy (chaperone mediated autophagy, CMA) and interacts with the cytosolic chaperone (HSC70), enabling its translocation to the lysosome with the help of Lamp2a, a receptor for CMA on the lysosomal membrane. It is not known whether GCase is a substrate for CMA or if CMA is affected in patients with PD and GD. **(4)** Macroautophagy could be affected. Accumulation of ubiquitinated proteins and p62 in the autophagosome inhibits fusion between the autophagosome and the lysosome, which augments the accumulation of autophagosomes in the cells. These eventually inhibit macroautophagy and impair lysosomal function. **(5)** Transcription factor EB (TFEB), a key regulator of lysosome biogenesis may play a role. Under normal conditions, mTOR interacts with TFEB on the surface of the lysosome, which leads to TFEB phosphorylation and cytosolic sequestration of this transcription factor. When autophagy is impaired or mTOR is inhibited, TFEB is no longer phosphorylated, which results in the dissociation of TFEB from the lysosome