Strategie innovative in ambito biologico: quali modelli?

Direttiva 2010/63 / UE

Iniziativa dei cittadini europei Stop Vivisection

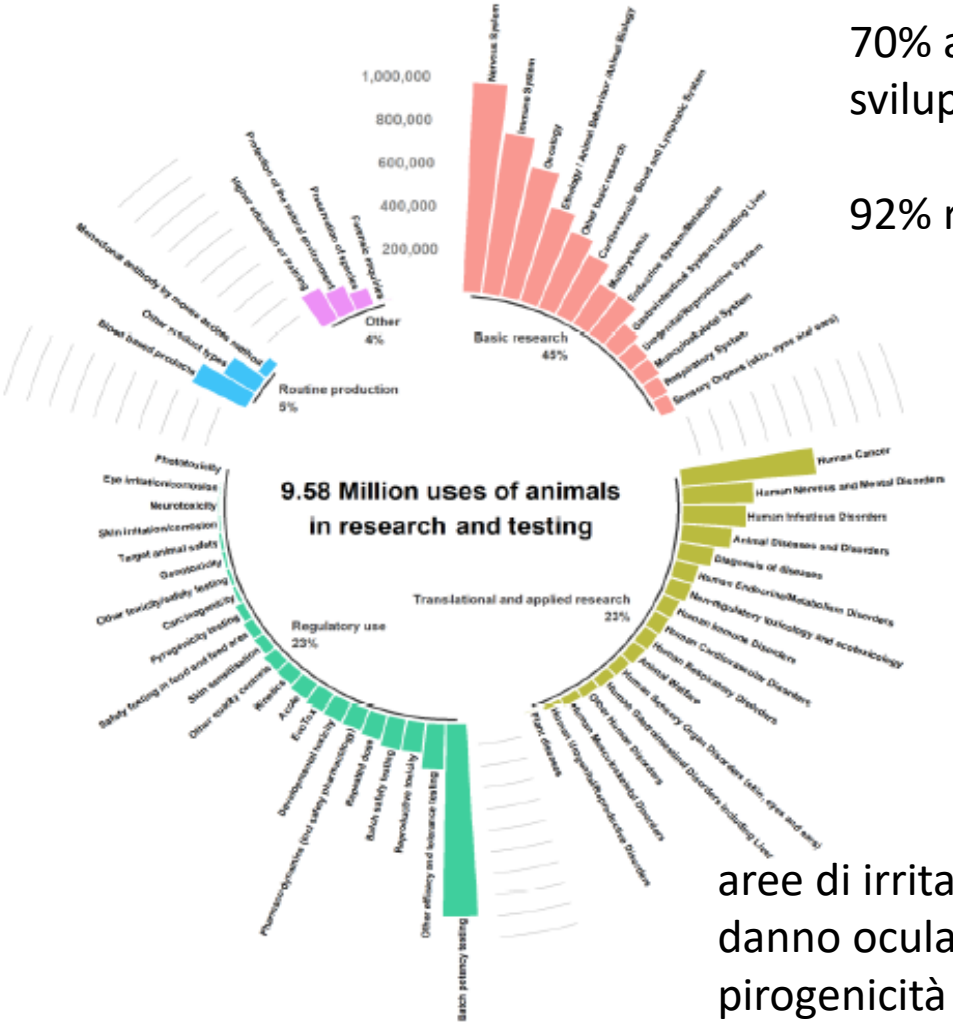
Rapporto statistico della Commissione sull'uso degli animali da laboratorio 2015-2017

- Numero di animali usati per la ricerca, testing, produzione, formazione: -2,1%
- Numero di animali usati per la creazione e il mantenimento di linee geneticamente modificate : -19,6%
- Totale animali usati in supporto alla ricerca e testing in Europa: -4,6%

La tossicità e altri test di sicurezza, compresa la farmacologia, hanno rappresentato l'8% di tutti gli usi degli animali

La maggior parte degli usi in quest'area erano correlati a

- tossicità riproduttiva
- tossicità a dosi ripetute
- farmacodinamica
- tossicità per lo sviluppo
- ecotossicità
- tossicità acuta e subacuta

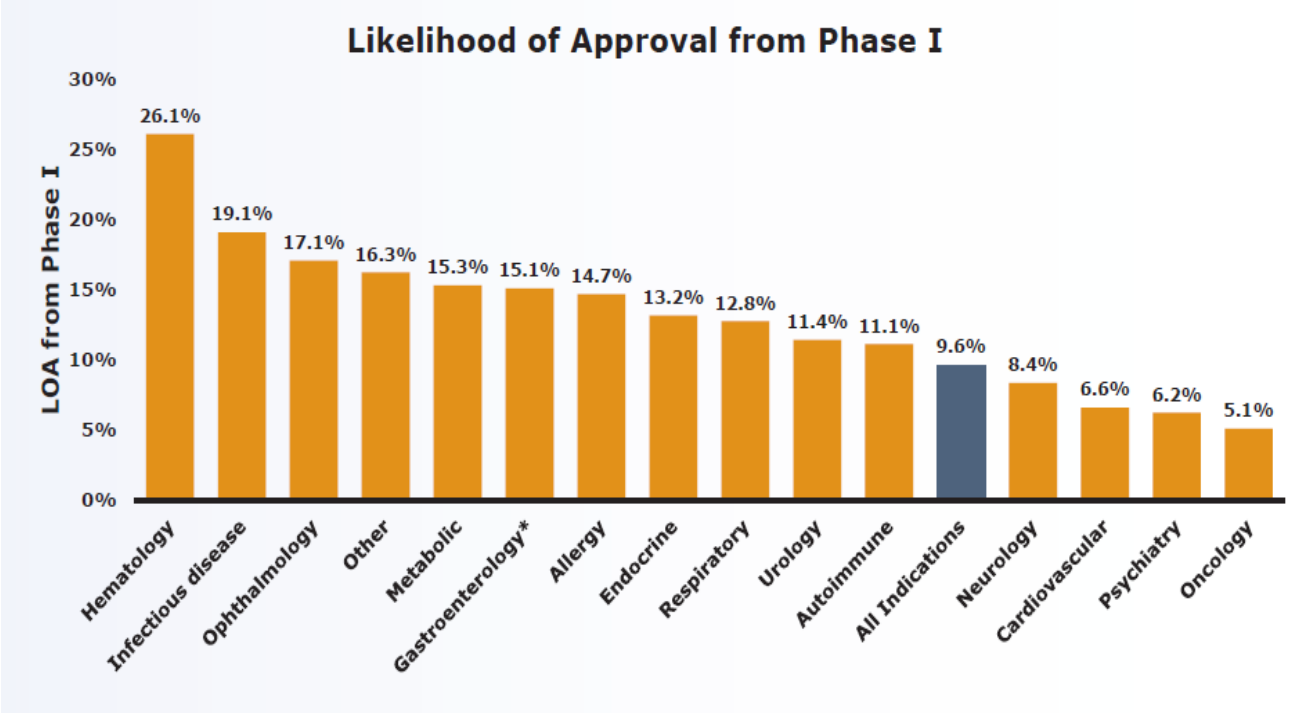


70% animali usati in ricerca di base e sviluppo dei farmaci

92% roditori, topi e ratti

aree di irritazione / corrosione della pelle, gravi danno oculare / irritazione oculare e test di pirogenicità

Sviluppo clinico



Un paradigma di ricerca fallito?

Animal Models of Alzheimer Disease: Historical Pitfalls and a Path Forward

Sarah E. Cavanaugh[1], *John J. Pippin*[1] *and Neal D. Barnard*[1,2]

[1]Physicians Committee for Responsible Medicine, Washington, D.C., USA; [2]Department of Medicine, George Washington University School of Medicine and Health Sciences, Washington, D.C., USA

(ALTEX. 2014;31(3):279-302.)

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 7, No. 26

Research Paper: Gerotarget (Focus on Aging)

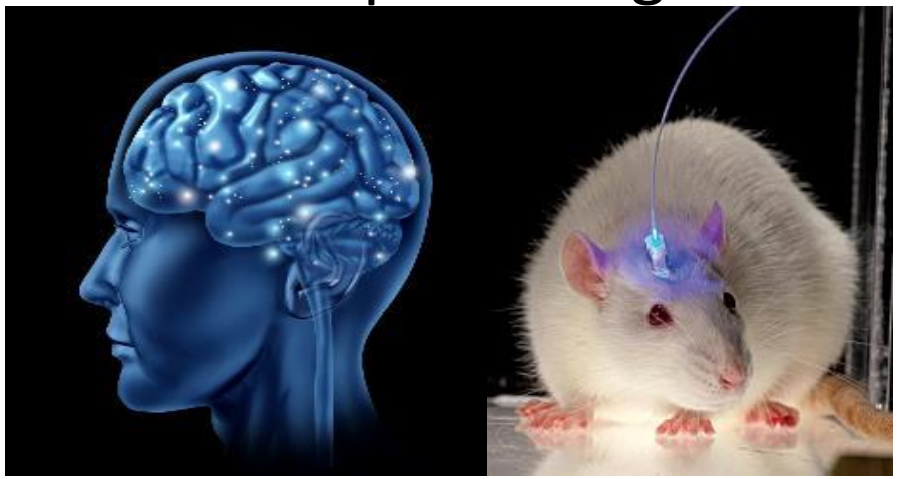
Alzheimer disease research in the 21st century: past and current failures, new perspectives and funding priorities

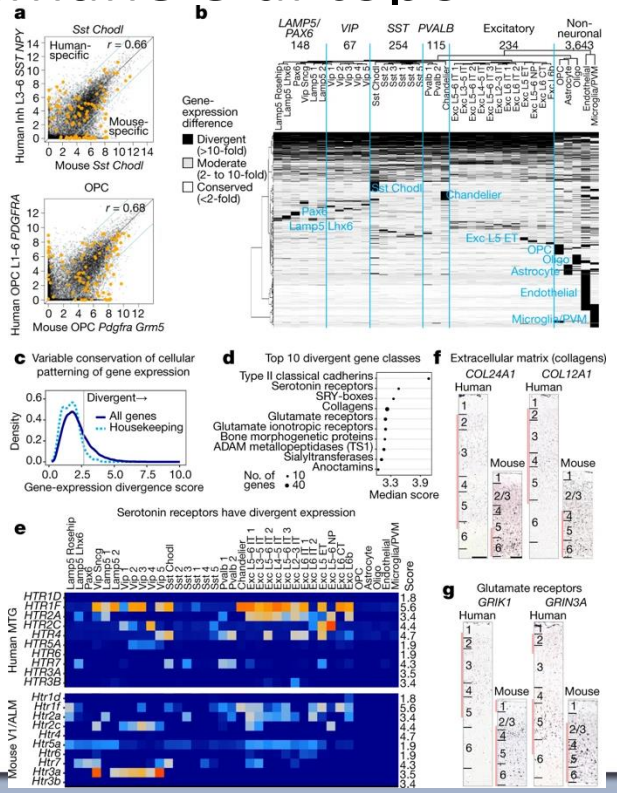
Francesca Pistollato[1], Elan L. Ohayon[2], Ann Lam[1,2], Gillian R. Langley[3], Thomas J. Novak[4], David Pamies[5], George Perry[6], Eugenia Trushina[7], Robin S.B. Williams[8], Alex E. Roher[9,10], Thomas Hartung[5], Stevan Harnad[11], Neal Barnard[1], Martha Clare Morris[12], Mei-Chun Lai[1], Ryan Merkley[1] and P. Charukeshi Chandrasekera[1]

Farmaci per la malattia di Alzheimer negli studi clinici statunitensi (https://www.alzforum.org)

Target types	Clinical trials	Approved	Inactive	Discontinued	Total
Amyloid-related	21	0	5	21	57
Cholesterol	2	0	1	0	3
Cholinergic system	3	4	5	18	30
Inflammation	14	0	3	8	25
Other neurotransmitters	16	1	1	19	37
Tau	11	0	1	4	16
Unknown	10	0	3	4	17
Other	39	0	6	13	58

Differenze tra tipi omologhi di cellule umane e di topo

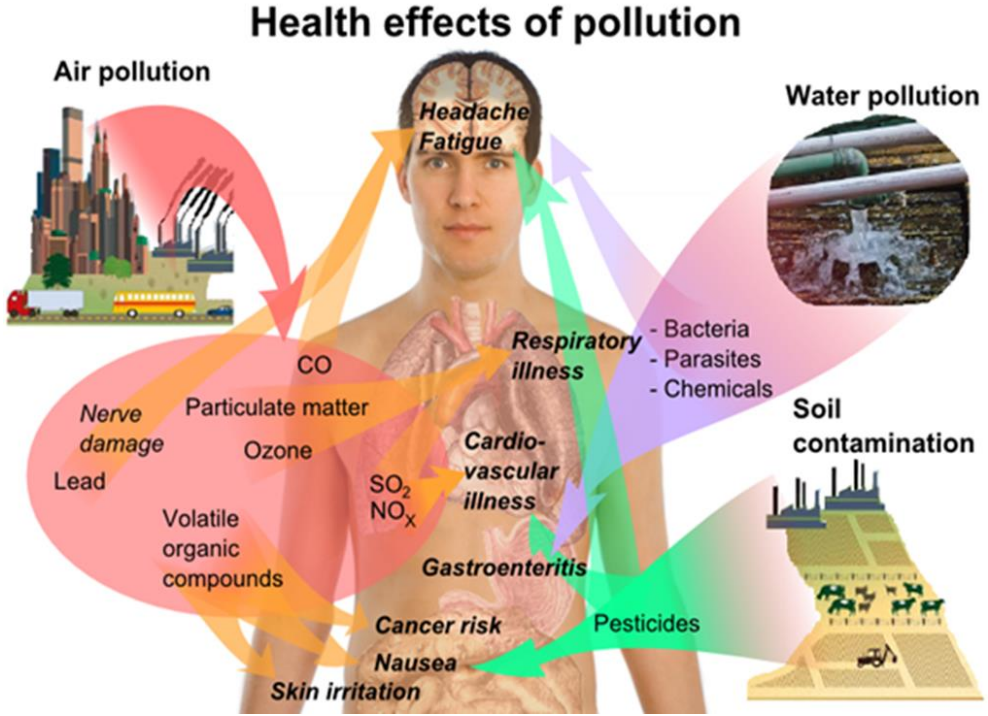




Conserved cell types with divergent features in human versus mouse cortex

Rebecca D. Hodge, Trygve E. Bakken, […]Ed S. Lein ,**Nature** volume 573, pages61–68(2019

Modelli avanzati in ricerca biomedica



- Incidenza / prevalenza di malattie umane
- Uso di modelli animali per lo studio di meccanismi o scoperta di farmaci
- Potenziale legame causale tra esposizione chimica / sviluppo della malattia

Modelli avanzati in ricerca biomedica

Asma, broncopneumopatia cronica ostruttiva (BPCO), fibrosi cistica

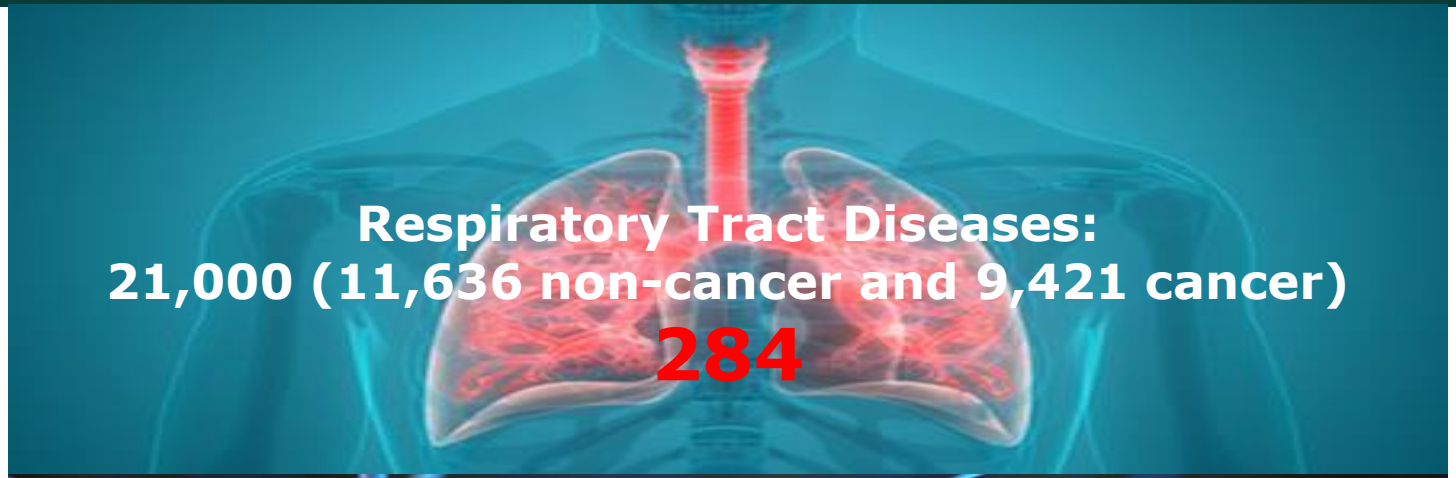
Malattie neurodegenerative (morbo di Parkinson e Alzheimer)

Risultati

- Catalogo dati del JRC
- Due relazioni tecniche

Messo a disposizione del pubblico sul sito web di EURL ECVAM su EU Science Hub alla fine del mese

Risultati preliminari



List of models

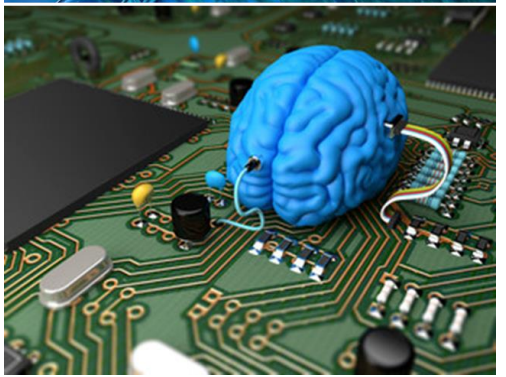
Year	Link to abstract	Disease area	Disease feature	Model - Category in DB Ecomole	Model type	Application/ aim	Biological or disease-specific endpoint	Status of the method/mo	Assay Throughput/ Content
2017	http://dx.doi.org/10.1016/j.neuron.2017.03.042	AD	Exploratory/ no specific feature	3b. Human/patient primary or stem cells	Non-differentiated human stem cells : iPSC	Disease mechanism (exp/theor)	Multiple biological endpoints	Under validation	Low-medium/medium
2013	http://dx.doi.org/10.1039/c2lc41033h	AD	Neuroinflammation	3g. Lab/brain on chip or microfluidic system	Co-culture model (multiple cells)	Model/method development - experim	Activation of microglia	Under development	Low-medium/medium
2017	10.1016/j.colsurfb.2017.08.020	AD	Protein aggregation	3f. Biochemical/cell-free assay	Other	Disease therapy developm	Protein dysfunction: amyloid peptide (any version)	Under development	Low-medium/low
2015	http://dx.doi.org/10.1016/j.jalz.2014.06.007	AD	Protein aggregation	3h. Computational/in silico	In silico model	Disease mechanism (exp/theor)	Protein dysfunction: amyloid peptide (any version)	under development	Low-medium/low
2017	10.1177/2472555217697964	AD	Protein aggregation	3f. Biochemical/cell-free assay	Proteins	Drug developm/ testing	Oxidative/nitrosative stress	Optimisation	Low-medium/low
2016	10.1038/srep39171	PD	Protein aggregation	3a. Human/patient ex-vivo tissue or body fluids (brain biopsy,	Brain (or CNS) tissue	Disease mechanism (exp/theor)	Protein dysfunction: Lewy bodies	Information not available	low-medium/low
2014	10.1016/j.jmb.2017.09.007	AD	Protein aggregation	3f. Biochemical/cell-free assay	Fibrils	Disease mechanism (exp/theor)	Protein dysfunction: Tau (phosphorylation)	Standardised	Low-medium/low
2017	10.1016/j.chempr.2017.09.011	AD	Protein aggregation	3h. Computational/in silico	In silico model	Disease therapy developm	Other	Under development	Low-medium/low
2017	http://dx.doi.org/10.1016/j.chempr.2017.09.011	AD	Protein aggregation	3f. Biochemical/cell-free assay	Fibrils	Disease mechanism (exp/theor)	Protein dysfunction: amyloid peptide (any version)	Under development	High (automatic)/low
2016	http://dx.doi.org/10.1111/ejn.13504	PD	na	3b. Human/patient primary or stem cells	Multipotent human stem cells: neuronal	Disease therapy	Multiple: cell chacterisation/differenti	Under development	

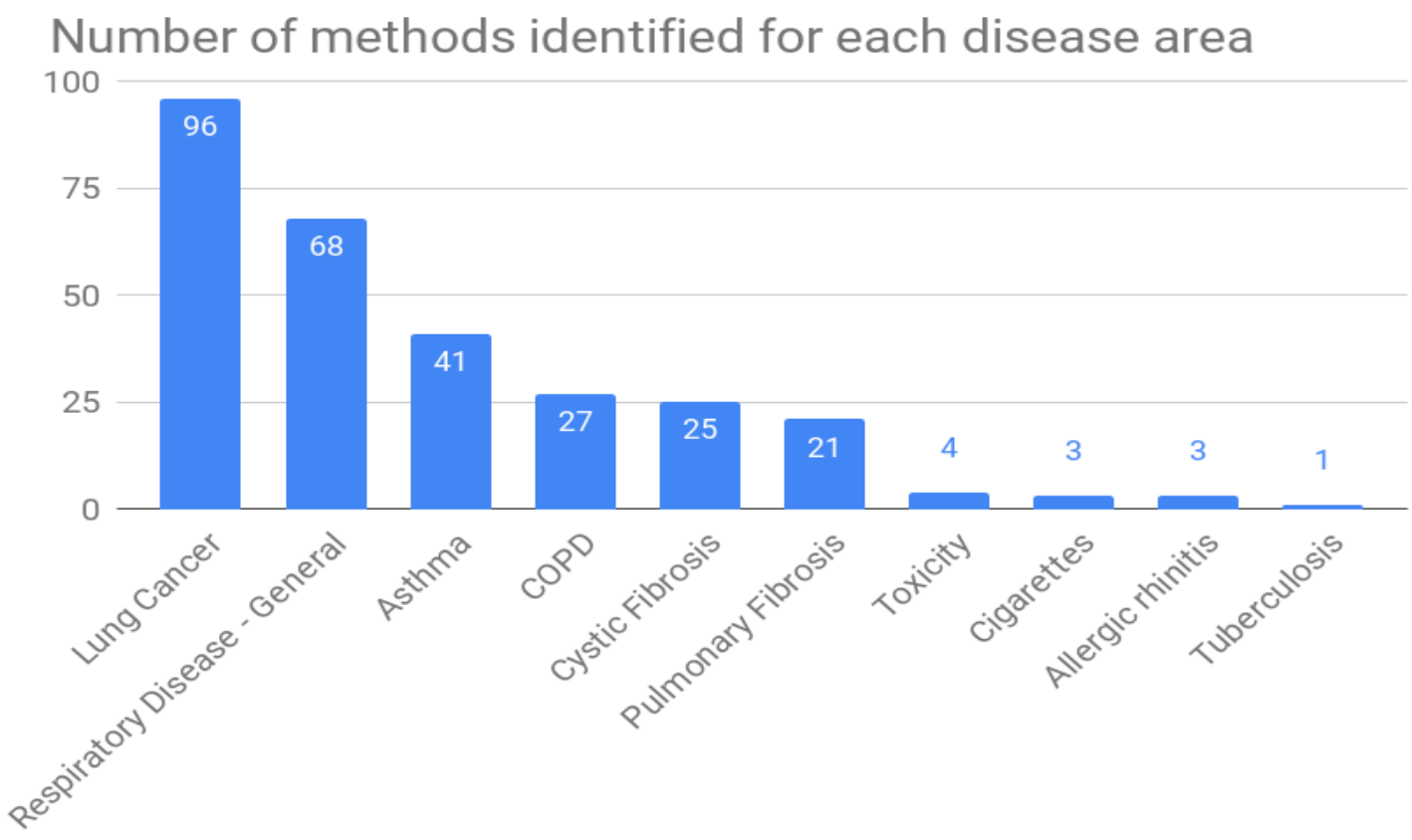
Prime osservazioni

Per le malattie respiratorie, i modelli che utilizzano linee cellulari stabilizzate sono ancora i più diffusi.

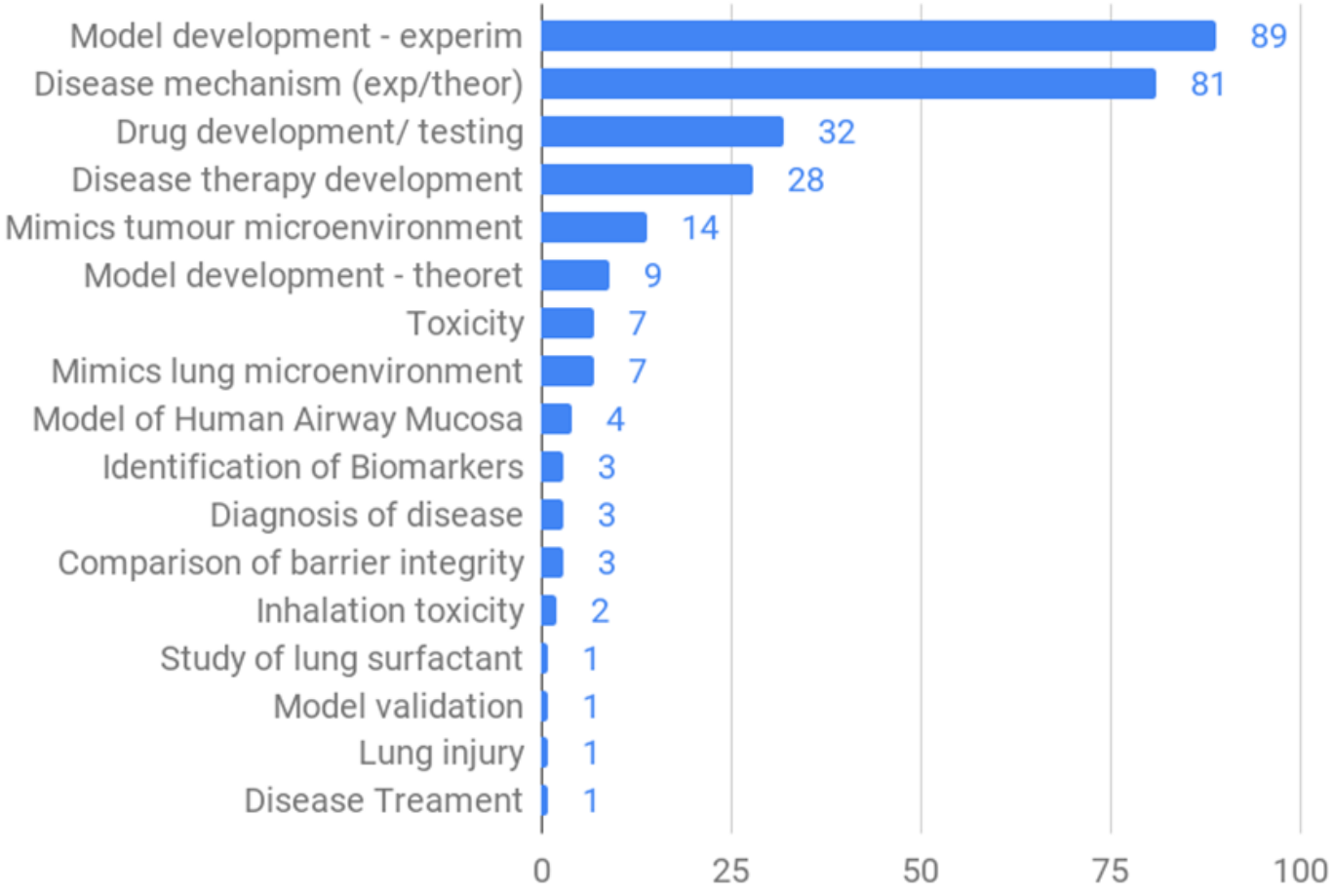
Per le malattie neurodegenerative, la maggior parte dei metodi inventariati è costituita da iPSC.

Modelli di malattia più rilevanti, come colture di tessuti umani 3D, sferoidi, organoidi e sistemi microfluidici / sono tra i piu' promettenti/rilevanti

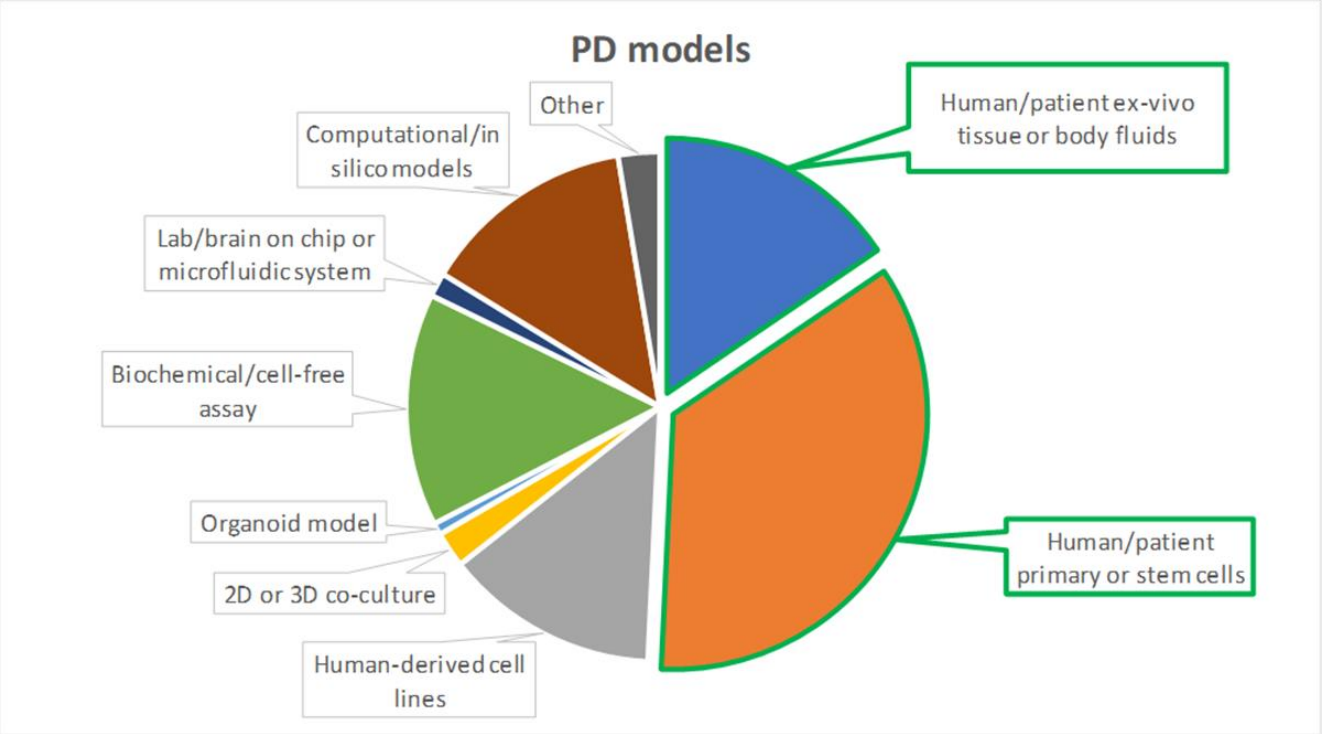


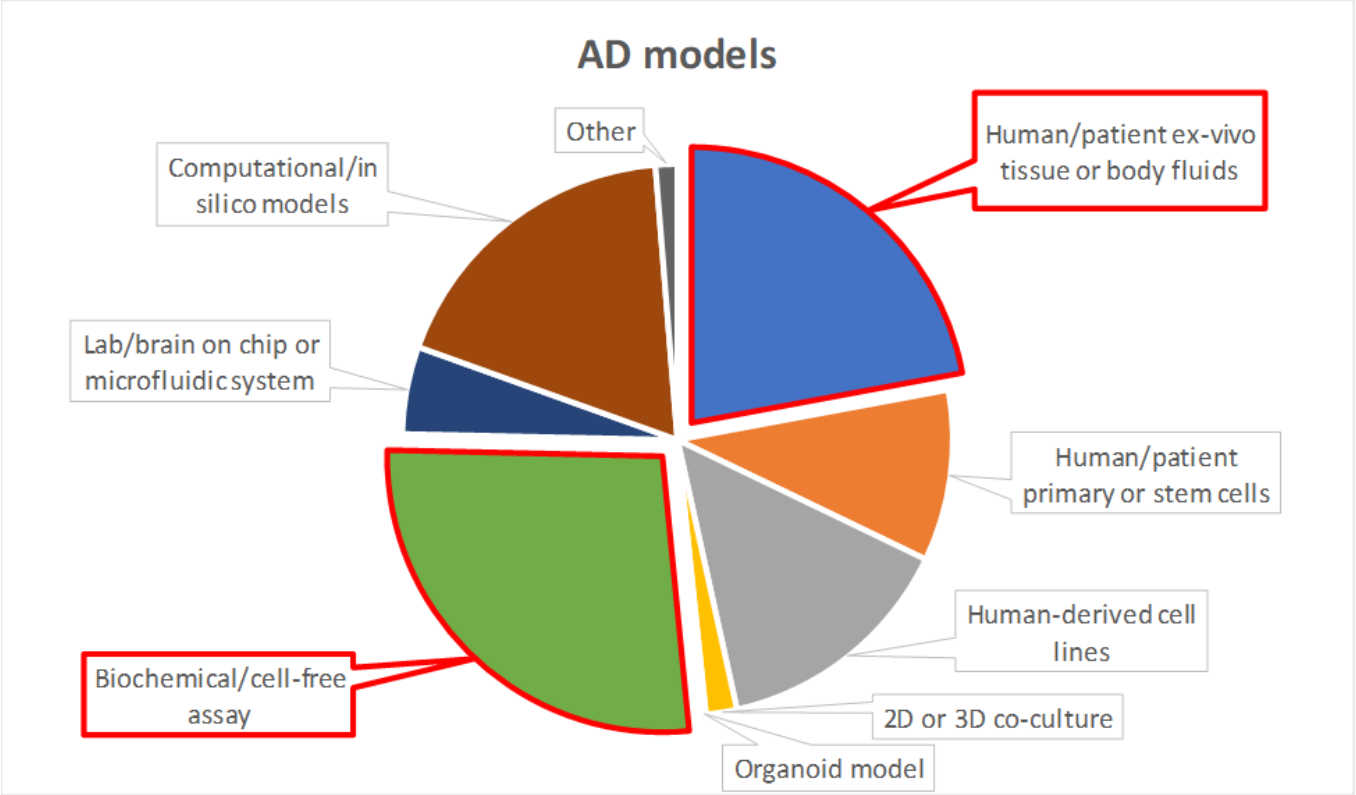

Number of methods identified for each disease area
100
75
50
25
0
96
68
41
27
25
21
4
3
3
1
Lung Cancer
Respiratory Disease - General
Asthma
COPD
Cystic Fibrosis
Pulmonary Fibrosis
Toxicity
Cigarettes
Allergic rhinitis
Tuberculosis

Number of methods identified broken down by application

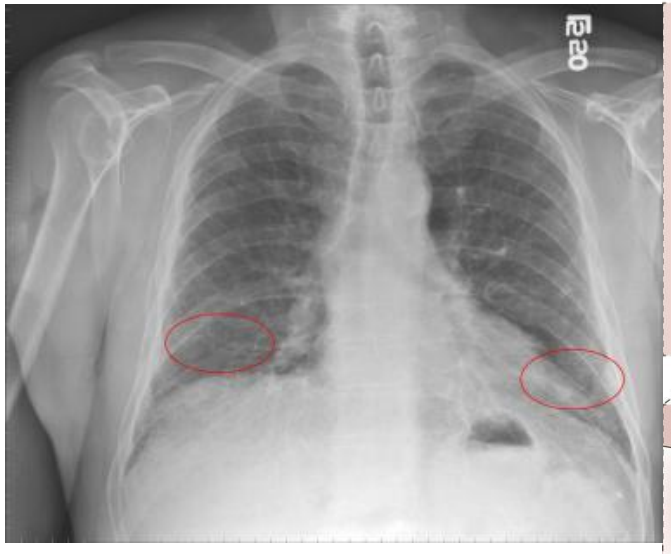


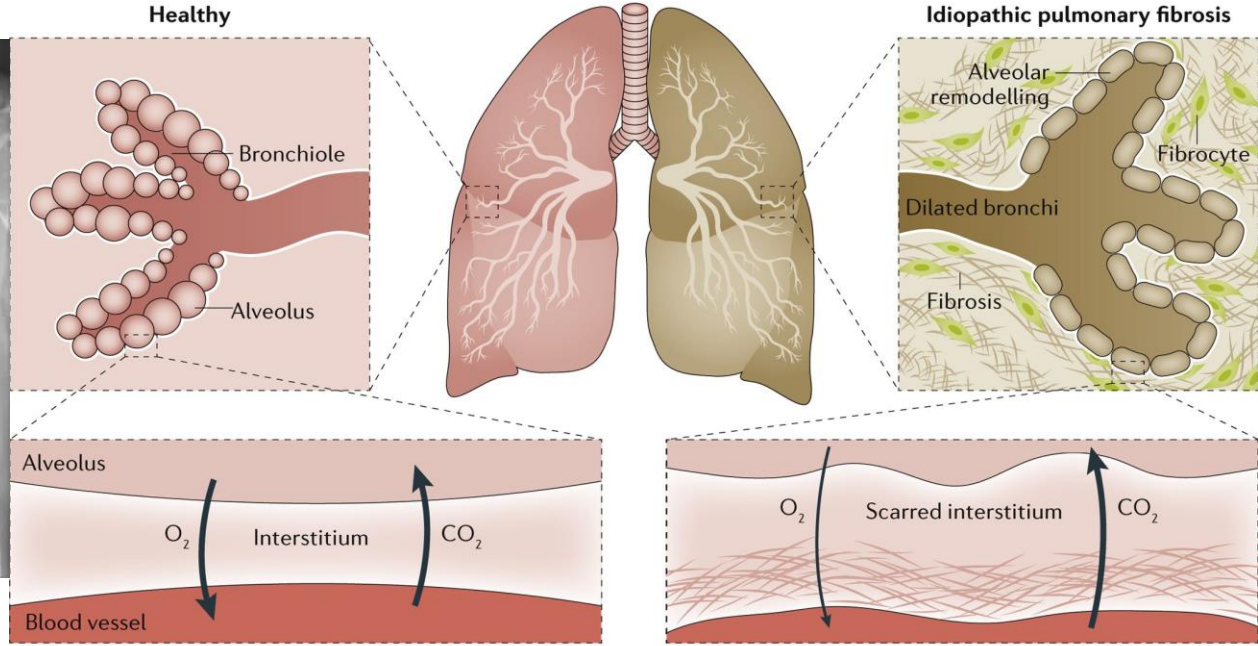
Meta analisi




AD models
Other
Human/patient ex-vivo tissue or body fluids
Computational/in silico models
Lab/brain on chip or microfluidic system
Human/patient primary or stem cells
Human-derived cell lines
Biochemical/cell-free assay
2D or 3D co-culture
Organoid model

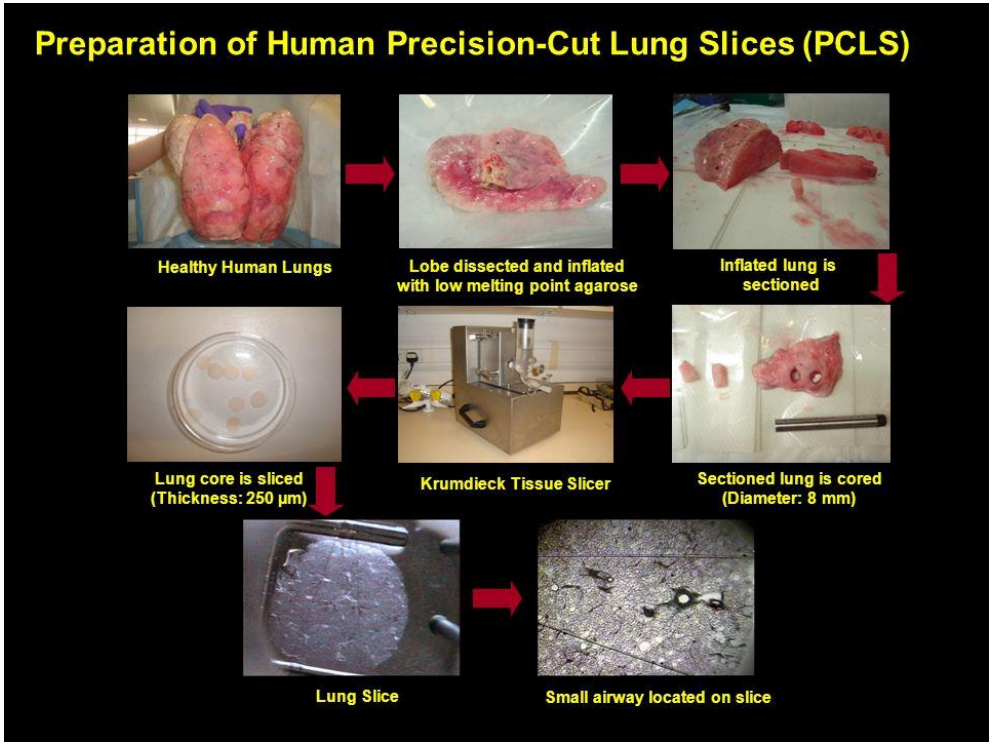
Fibrosi polmonare idiopatica (IPF)

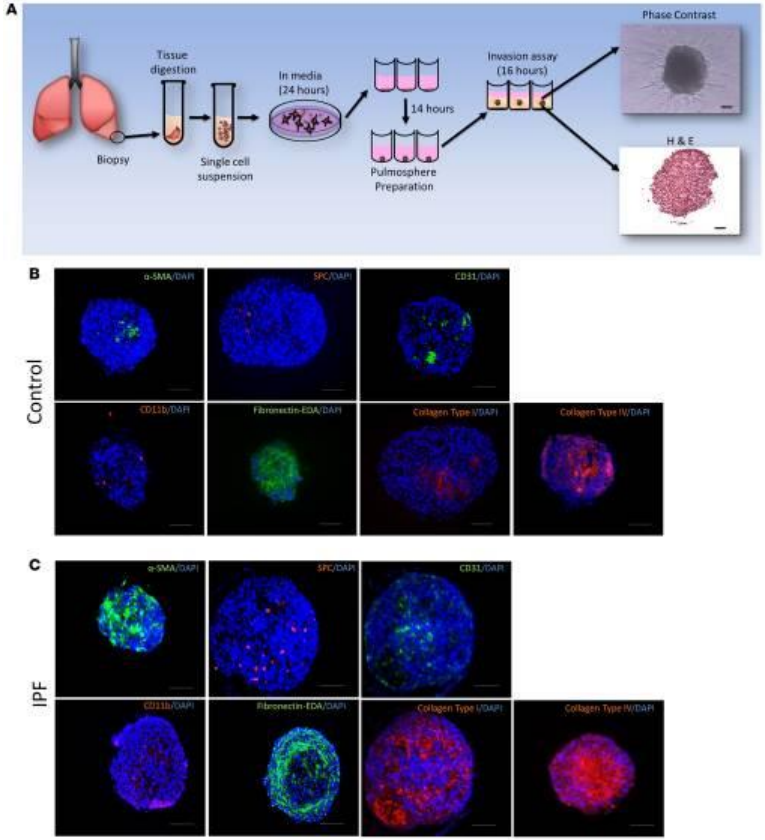


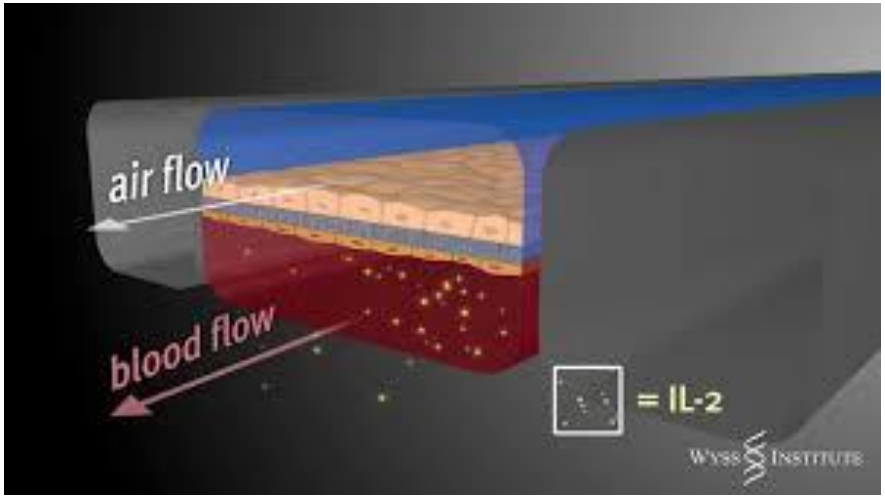


Nature Reviews | Disease Primers

Modelli avanzati di IPF



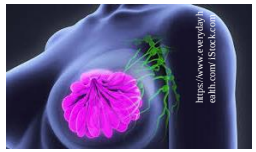

A
Tissue digestion
Biopsy
Single cell suspension
In media (24 hours)
14 hours
Pulmosphere Preparation
Invasion assay (16 hours)
Phase Contrast
H & E
B
Control
α-SMA/DAPI
SPC/DAPI
CD31/DAPI
CD11b/DAPI
Fibronectin-EDA/DAPI
Collagen Type I/DAPI
Collagen Type IV/DAPI
C
IPF
α-SMA/DAPI
SPC/DAPI
CD31/DAPI
CD11b/DAPI
Fibronectin-EDA/DAPI
Collagen Type I/DAPI
Collagen Type IV/DAPI


air flow
blood flow
= IL-2
WYSS INSTITUTE

Review of non-animal models in use for biomedical research

2nd Call on February 2019

Cardiovascular diseases

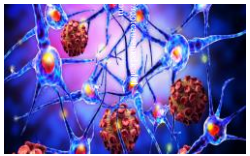


Breast cancer

Immune Oncology Models

5 new biomedical areas

Immunogenicity testing for advanced therapy medicinal products



Autoimmune diseases

Utenti target

- Gruppi di ricerca che presentano una proposta di progetto che utilizza animali vivi;
- Organismi di benessere degli animali che forniscono consulenza ai gruppi di ricerca sulle proposte di progetto;
- Autorità competenti responsabili della valutazione del progetto;
- Comitati nazionali che facilitano un approccio coerente alla valutazione dei progetti, alla diffusione delle informazioni e alla condivisione delle migliori pratiche all'interno di ciascuno Stato membro;
- Punti di contatto nazionali, responsabili dell'attuazione della direttiva negli Stati membri.

Grazie!

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