Expediting Drug Discovery for Undruggable Targets Using AI

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The Centre for Misfolding Diseases

We established the Centre for Misfolding Diseases in 2014
with the mission is to discover the molecular origins of misfolding diseases
and to use this knowledge to develop methods to combat them.

The Chemistry of Health Laboratory

Since 2018, Centre for Misfolding Diseases is hosted
in the Chemistry of Health Laboratory in central Cambridge.

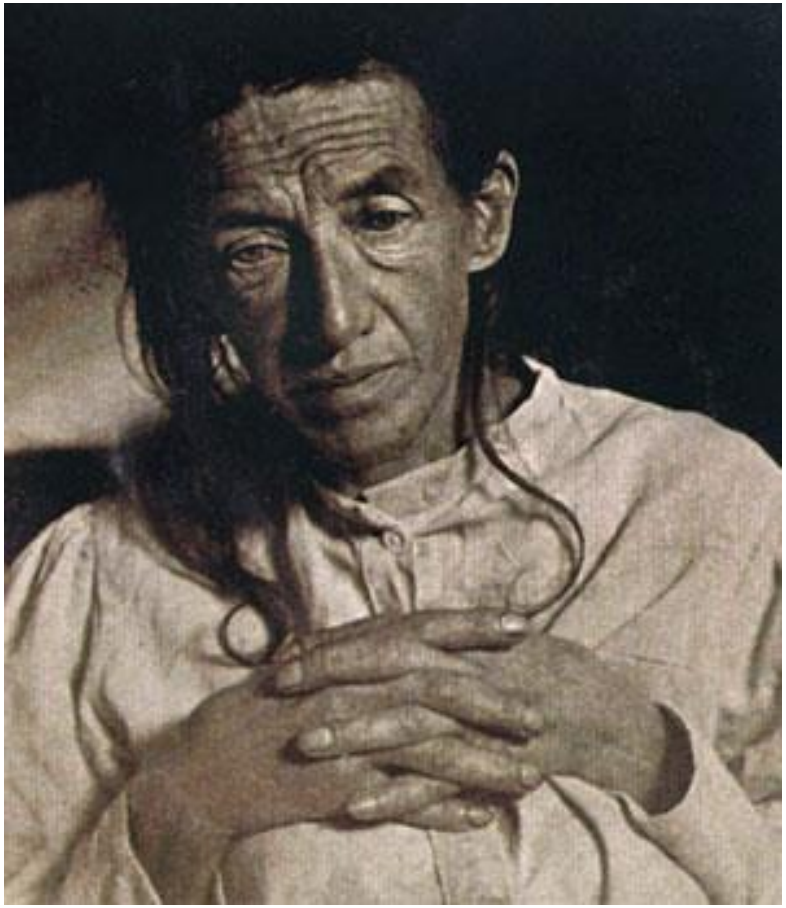
The Chemistry of Health Laboratory was funded through a UK program
to promote early-stage partnerships between academia and industry.

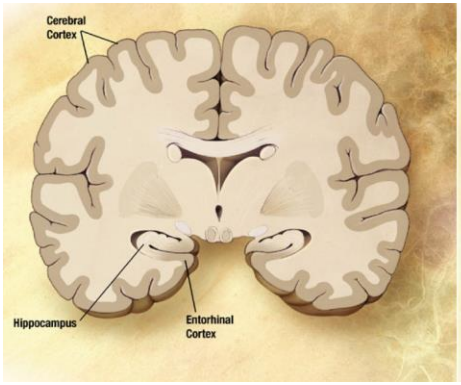
The Chemistry of Health Incubator

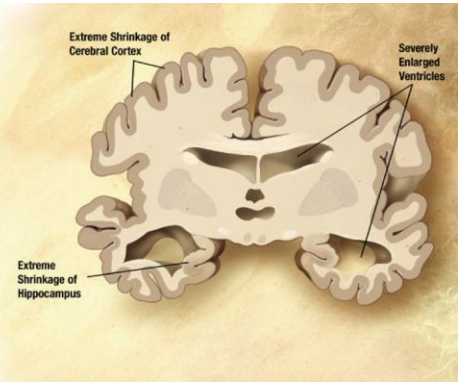
Chemistry of Health hosts a state-of-the art incubator space to facilitate the translation into clinical applications of the research carried out in the University of Cambridge.

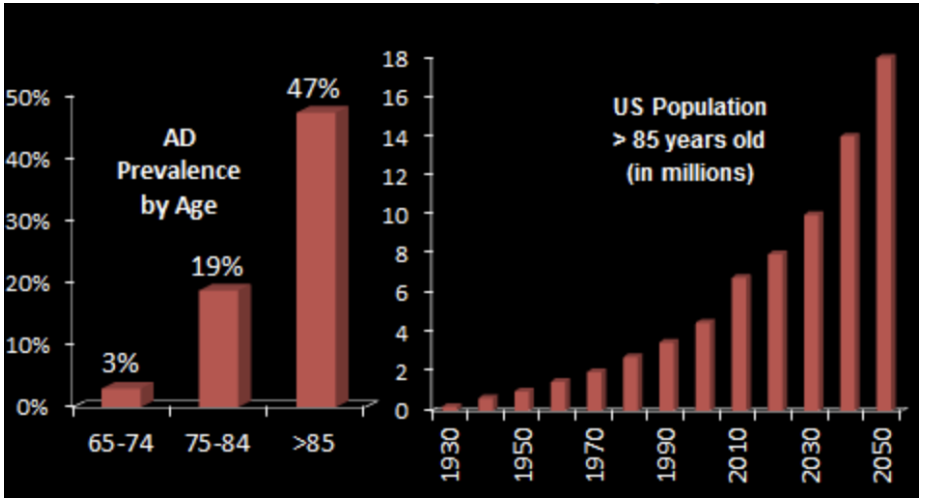
This Chemistry of Health Incubator hosts spin-out companies that focus on the development of analytical, diagnostic and therapeutic tools.

Alzheimer's disease

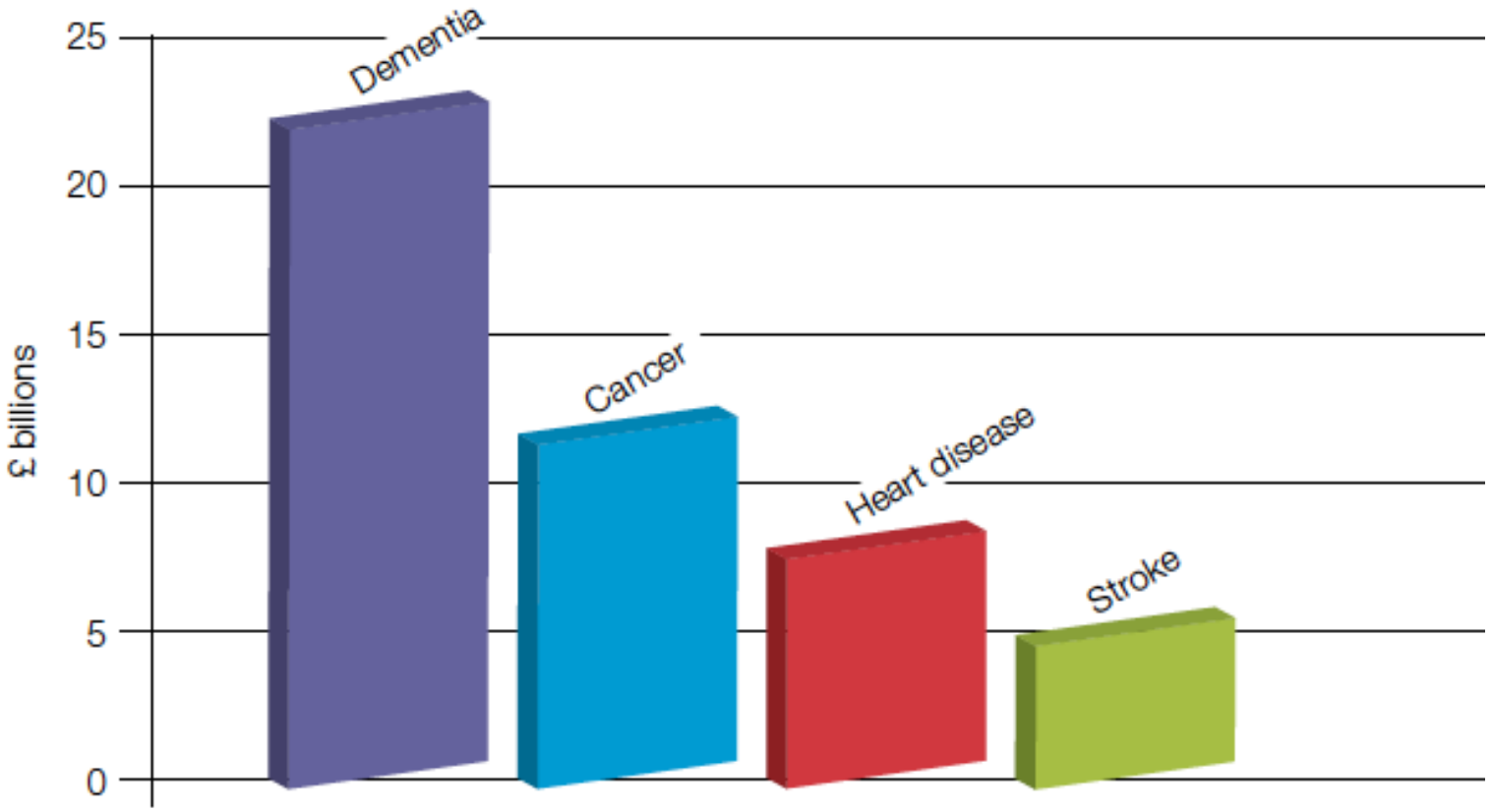








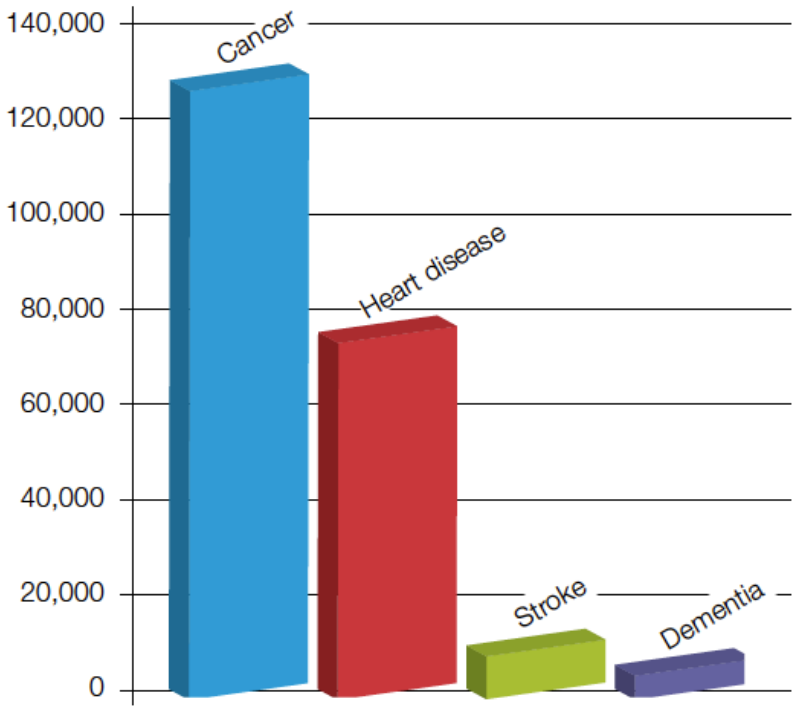
Social costs of dementia



The annual cost of dementia is larger than that of cancer and heart disease combined (UK data).

Source: Alzheimer's Research Trust

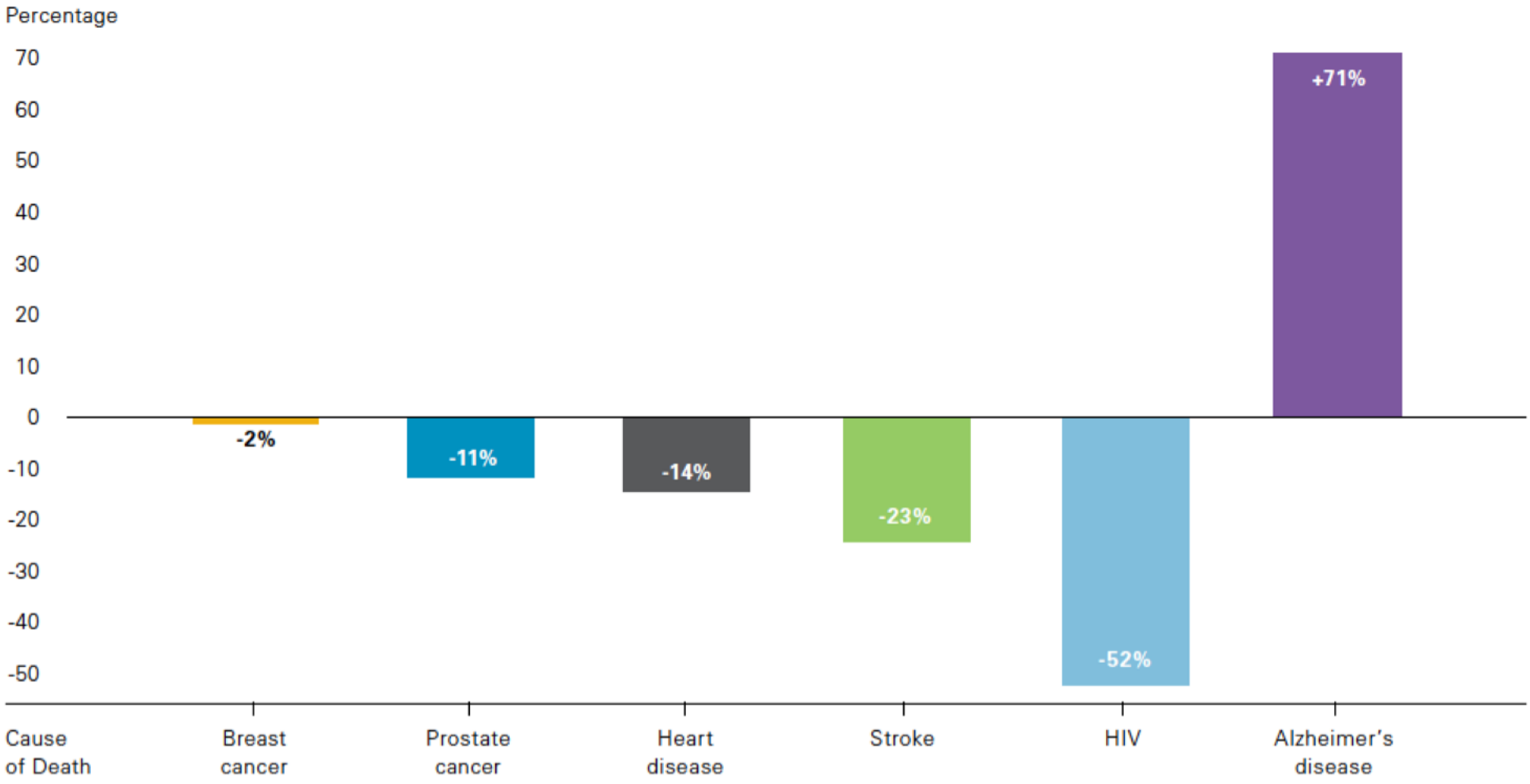
Funding dementia research



Dementia receives ten times less research funding than cancer,
despite causing a similar number of deaths
and costing twice as much to our healthcare system.

Source: Alzheimer's Research Trust

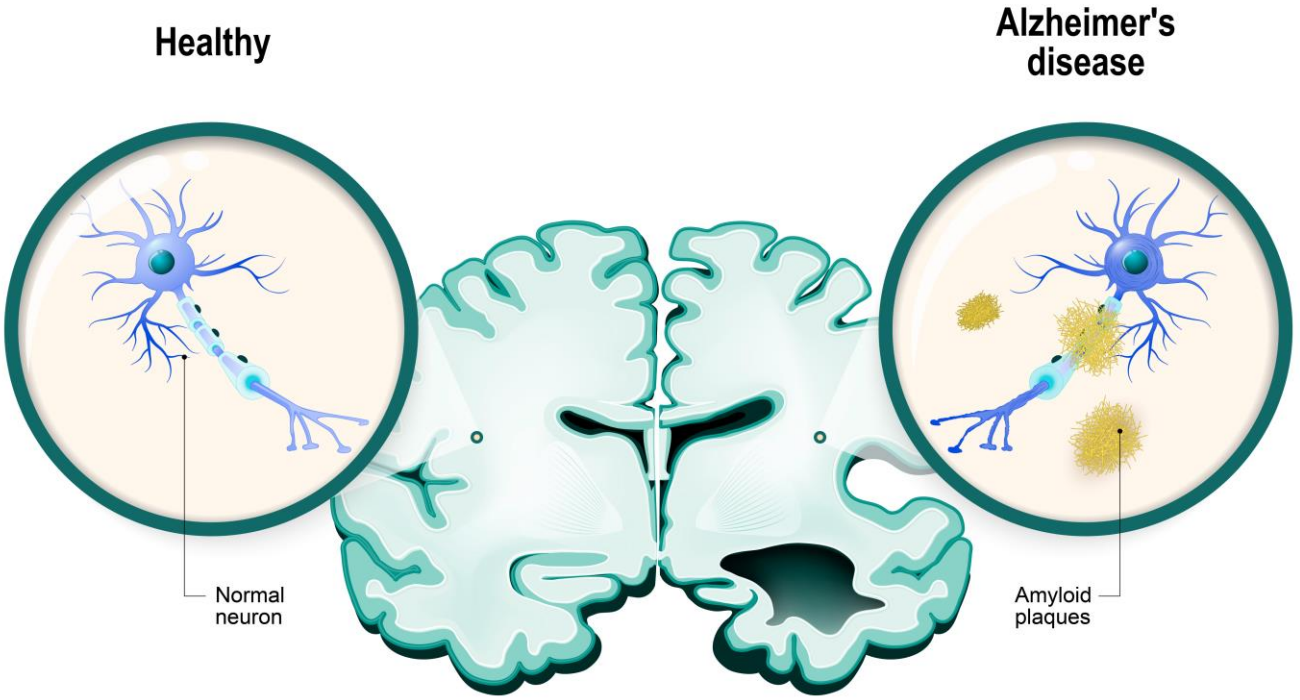
Percentage Changes in Selected Causes of Death (All Ages) Between 2000 and 2013



Among the leading causes of death worldwide, this condition is currently the only one that we cannot prevent, cure or even slow down.

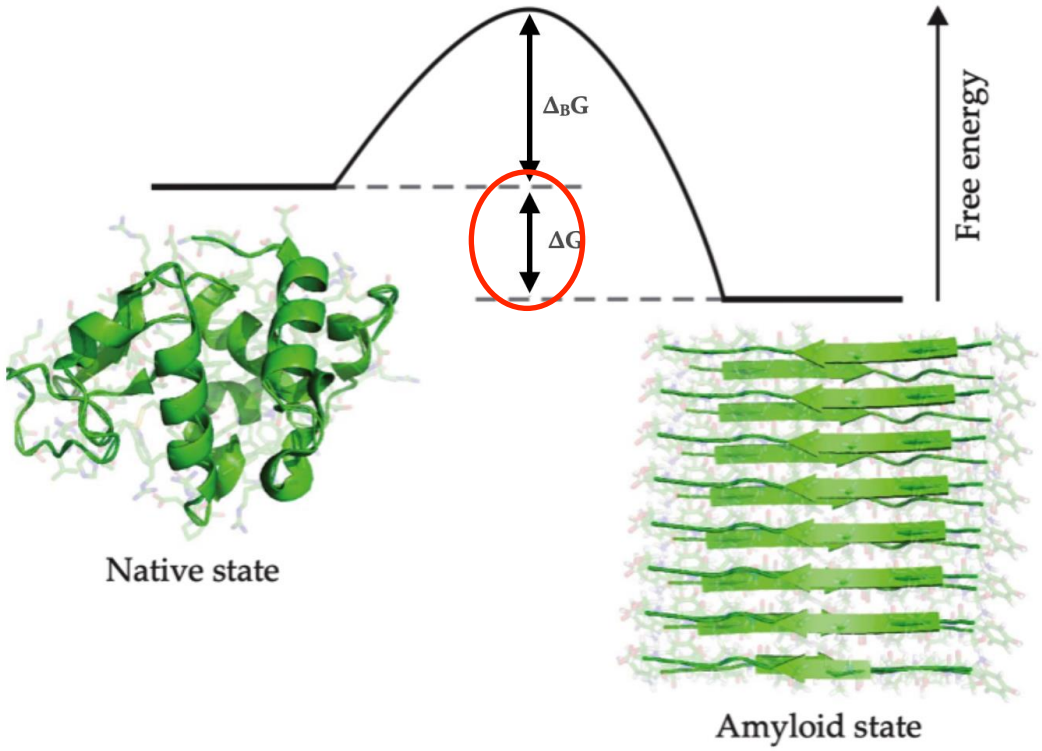
Source: Alzheimer's Association 2015

Alzheimer’s disease is associated with protein aggregation



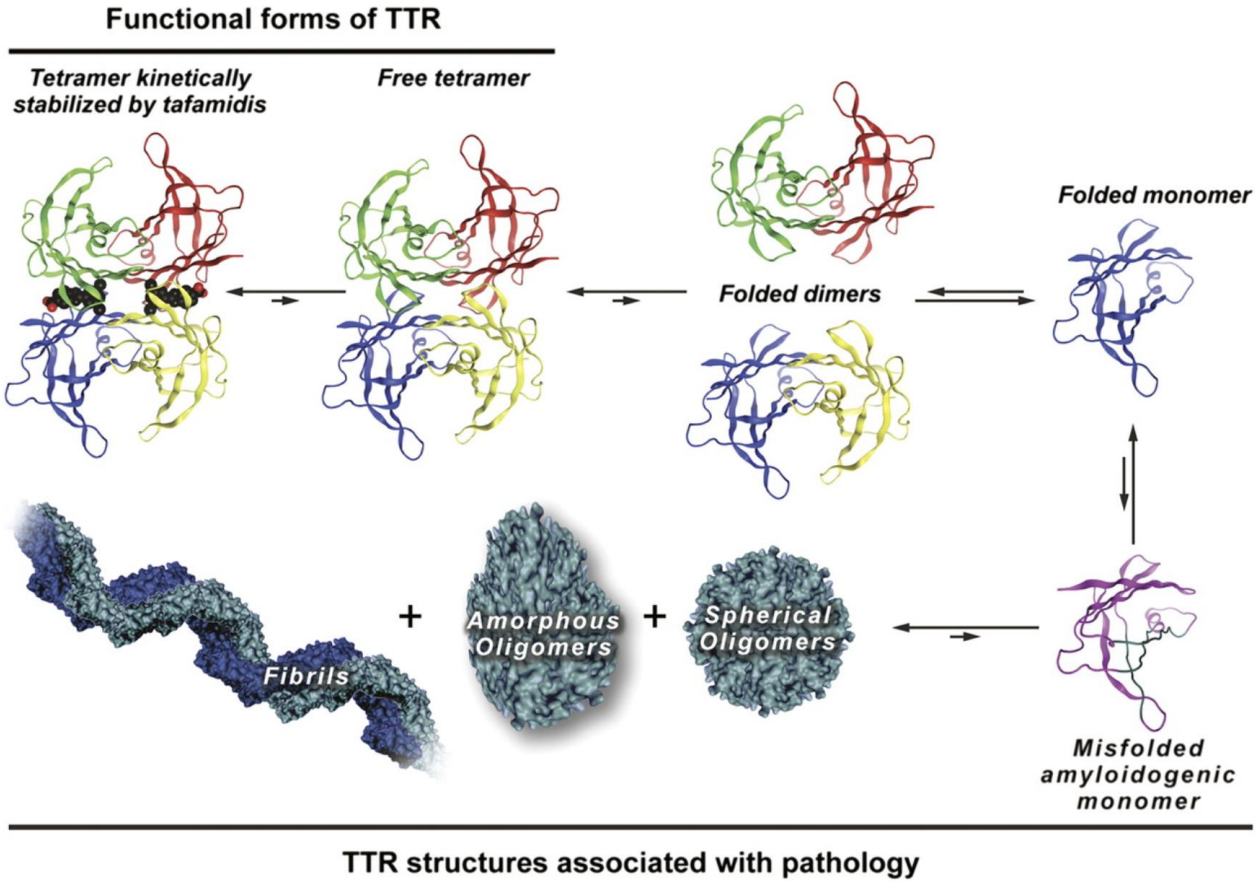
The molecular hallmarks of Alzheimer’s disease are aberrant protein deposits, primarily formed by Aβ (amyloid plaques) and by the protein tau (neurofibrillary tangles).

Drug discovery to prevent protein aggregation



We restore the stability of the native state by pharmacological chaperones

Tafamidis prevents the aggregation of transthyretin

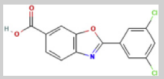
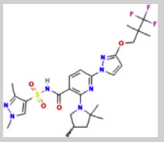
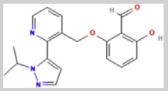


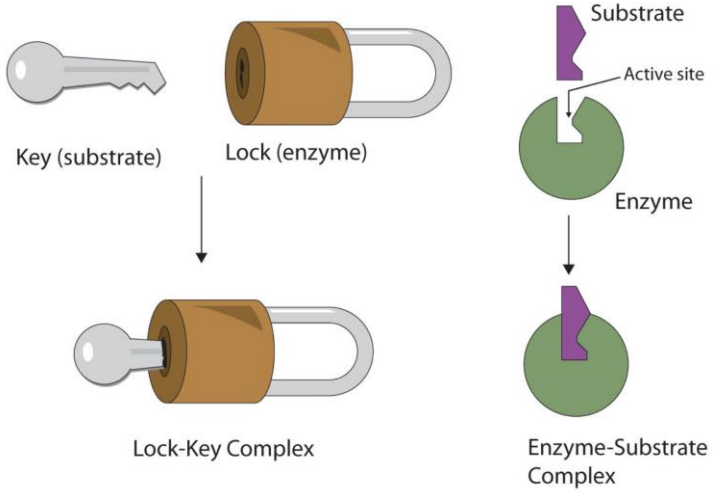
Tafamidis is an approved drug for transthyretin familial amyloid polyneuropathy.

It has the mechanism of action of a pharmacological chaperone.

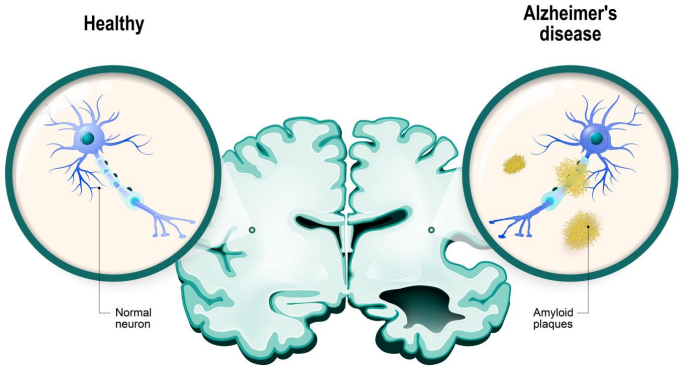
Approved drugs that prevent misfolding and aggregation by stabilising the native state

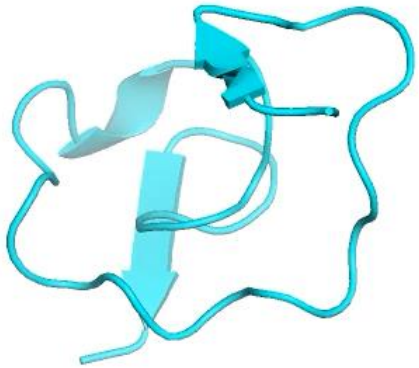
Drugs approved by the FDA/EMA for the treatment of protein misfolding diseases.

Protein misfolding disease	Protein name	Drug name	Brand name	Chemical structure	Mechanism of action	Year of FDA approval	Year of EMA approval
Transthyretin amyloidosis (ATTR)[a]	Wild-type or Mutant TTR[a]	Tafamidis	Vyndaqel® or Vyndamax®		Binding to the two thyroxine binding sites of native tetrameric TTR endowing TTR with thermodynamic and kinetic stability	2019[e]	2011[f] and 2020[g]
Fabry disease (FD)[b]	Mutant α-GAL A[b]	Migalastat or DGJ	Galafold®		Binding to the active site of the fully folded enzyme (α-GAL A) with consequent stabilization	2018	2016
Cystic fibrosis (CF)[c]	F508del mutant CFTR[c]	Ivacaftor (VX-770) Tezacaftor (VX-661) elexacaftor (VX-445)	Trikafta® or Kaftrio®		Ivacaftor promotes channel gating of CFTR, whereas the correctors putatively bind to distinct domains of CFTR enabling their folding	2019[c]	2020[c]
Sickle cell disease (SCD)[d]	Hb with E6V in β-chain (HbS)	Voxelotor or GBT440	Oxbryta®		Covalent/reversible binding of the aldehyde group with the α-chain N-terminus of oxy-HbS to prevent deoxy-HbS polymerization	2019	pending



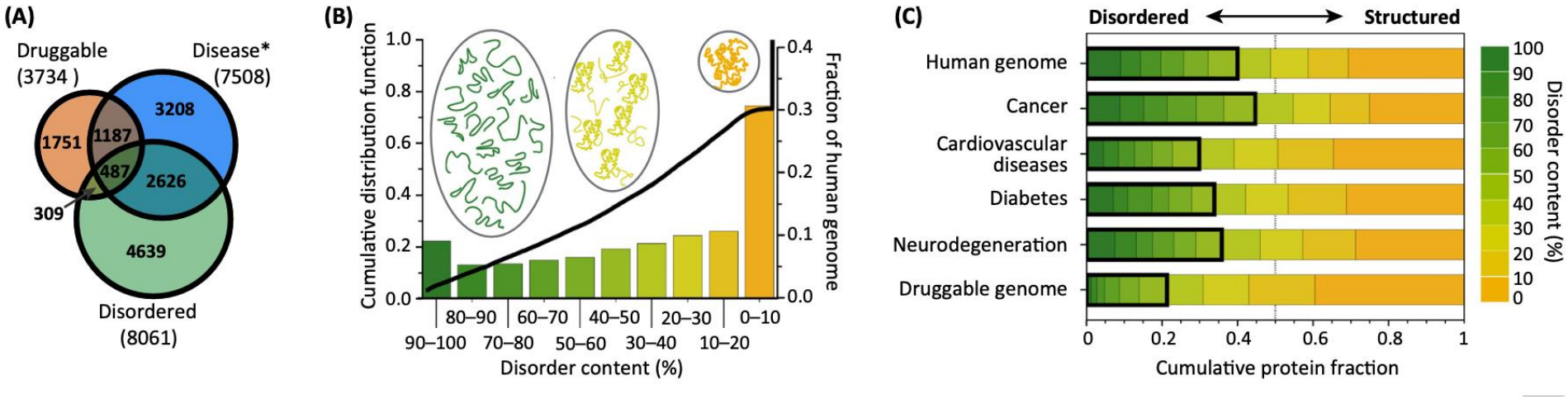
Stabilisation of the native states of disordered proteins





Challenge: There are no stable binding pockets

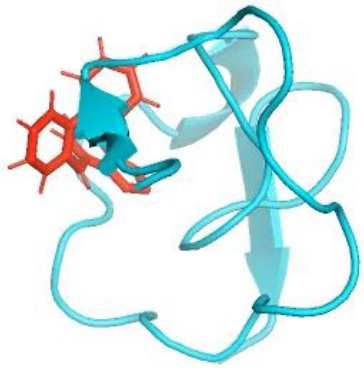
Disordered proteins make up 1/3 of the human proteome



Disordered proteins are considered undruggable

Heller et al. TiBS 2015

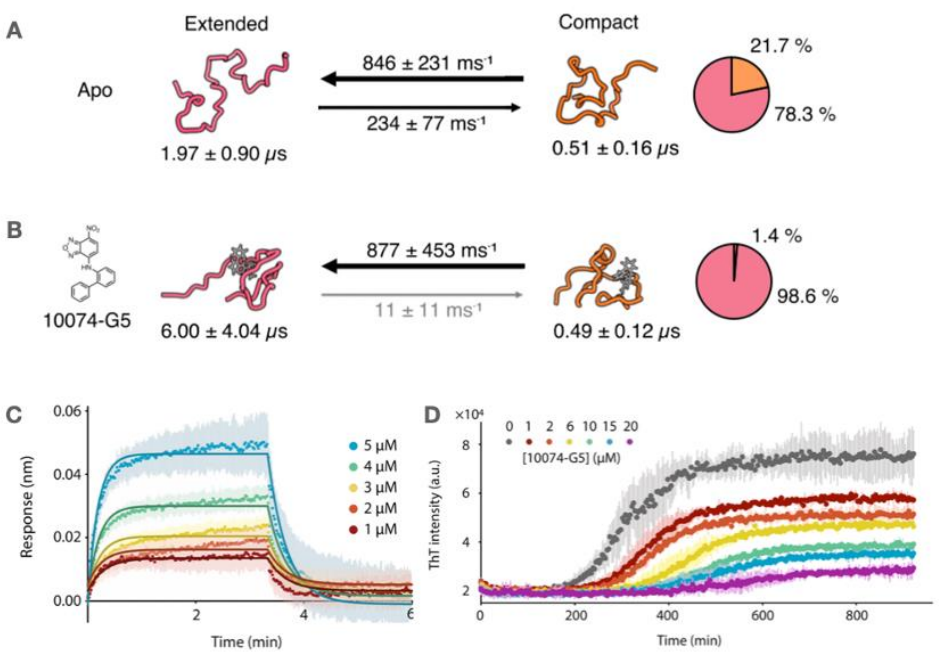
Disordered binding

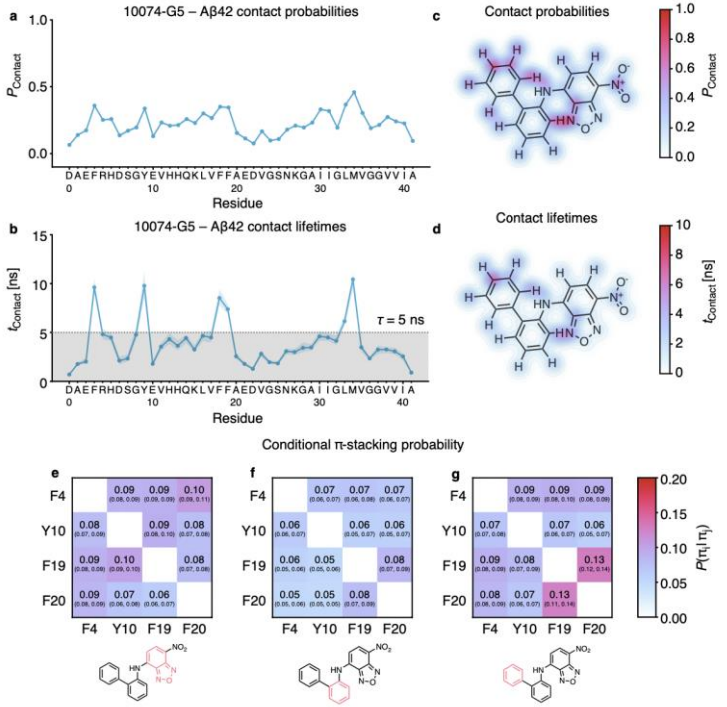


Drug binding is enhanced by an increase in entropy

$F = E - TS$

Stabilisation of the native state of Aβ: 10074-G5



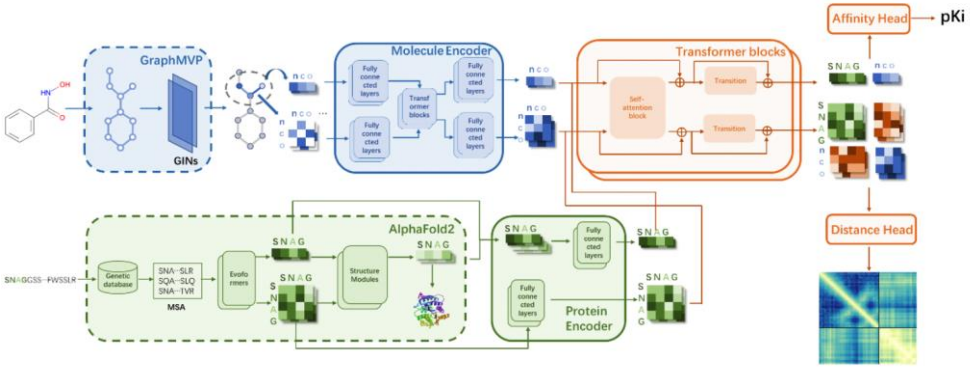


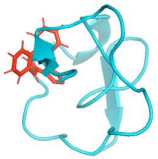
The small molecule 10074-G5 binds Aβ monomers, stabilises the native disordered state, and inhibits Aβ aggregation in a dose-dependent manner

Heller et al Sci. Adv. 2020
Lohr et al Nature Comp. Sci. 2021
Lohr et al ACS Chem. Neurosci. 2022

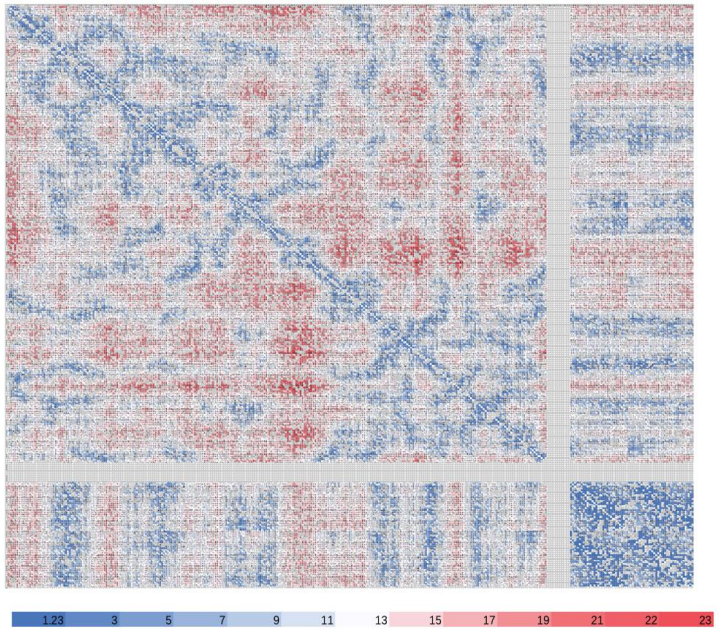
AlphaFold predictions of protein structure

Transformer-based screening of pharmacological chaperones

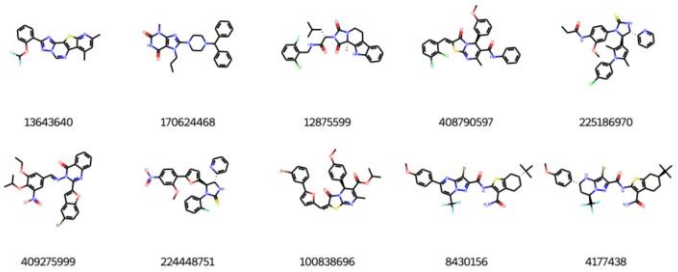




Ligand-protein distance matrix

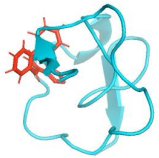


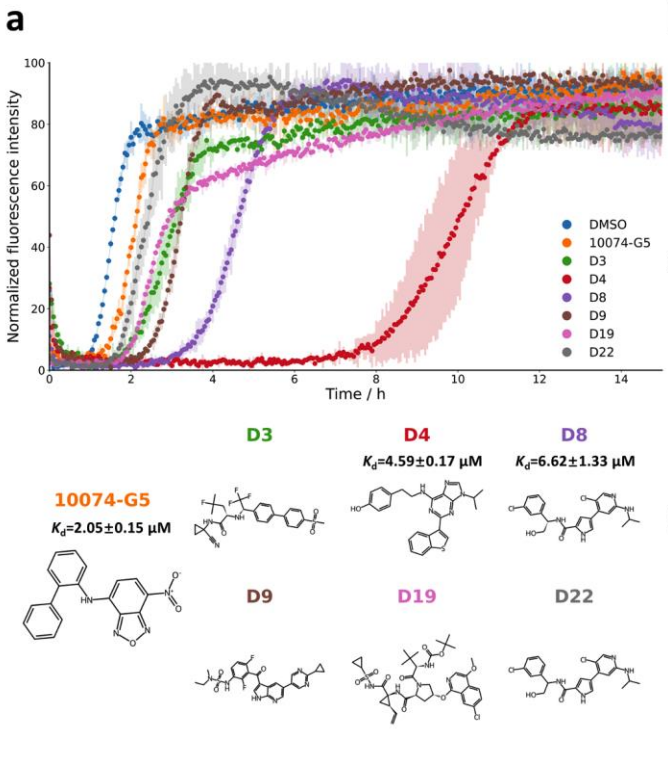
AI replaces the high-throughput experimental screening of large chemical libraries

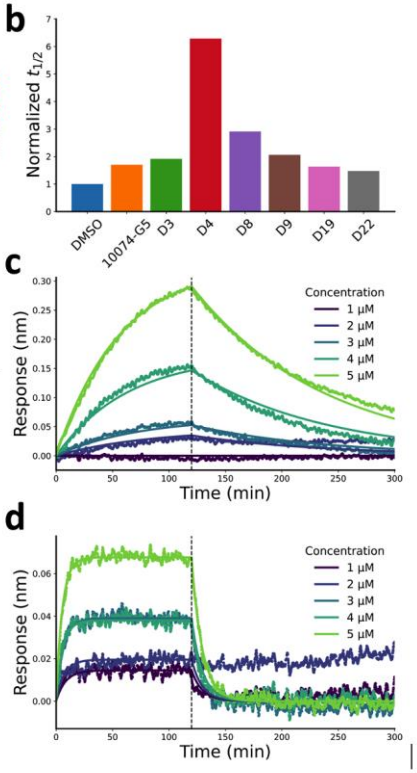


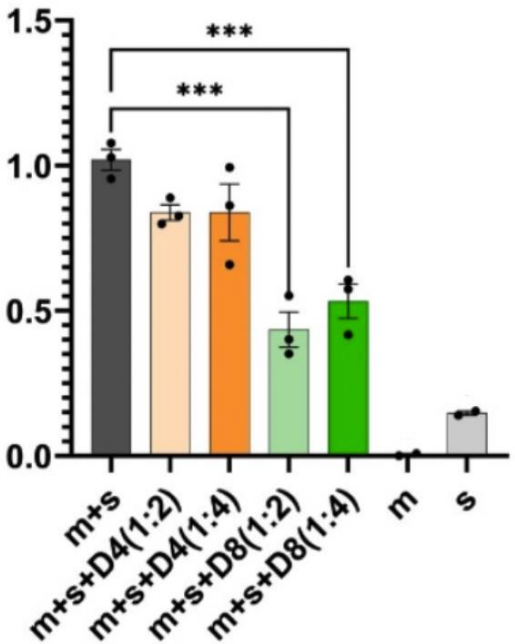
Zhang et al. bioRxiv 2023.11.27.568880

AI-driven discovery of pharmacological chaperones for Aβ in Alzheimer's disease









In vitro aggregation assay

In vitro binding assay

iPSC-derived cortical neurons

Zhang et al. bioRxiv 2023.11.27.568880

Ligand-Transformer unlocks undruggable targets

Our current targets include:

- A**β** (Alzheimer's)
- **α**-synuclein (Parkinson's)
- tau (Alzheimer's)
- TDP-43 (ALS)
- mHTT exon1 (Huntington)
- prion protein (prion disease)
- p53 (cancer)
- c-myc (cancer)
- kinases (cancer)

Alzheimer's failures in clinical trials

AI is creating transformative tools to address this challenge

Acknowledgements

Dillon Rinauro
Magda Nowinska
Marc Oeller
Michele Perni
Benedetta Mannini
Patrick Flagmeier
Tessa Sinnige
Giuliana Fusco
Mauricio Aguilar Rangel
Katarina Pisani
Alicia Gonzales-Diaz
Gabi Heller
Georg Meisl
Faidon Brotzakis
Michael Metrick
Alessia Santambrogio
Samuel Dada
Thomas Michaels
Roxine Staats
Simone Ruggeri
Sean Chia
Rob Horne
Andrea Possenti
Celine Galvagnion
Alex Buell
Phil Lindstedt
Ross Taylor
Alyssa Miller
Thomas Lohr
Klara Kulenkampff
Maarten Hardenberg
Florian Buhr
Mauricio Aguilar Rangel
Shengyu Zhang

Chris Dobson (Cambridge)
Tuomas Knowles (Cambridge)
Sara Linse (Lund)
Johnny Habchi (Cambridge)
Sam Cohen (Cambridge)
Pietro Sormanni (Cambridge)
Francesco Aprile (Imperial College)
John Christodoulou (UCL)
Rick Morimoto (Northwestern)
Ulrich Hartl (Max Plank)
Fabrizio Chiti (Florence
Dave Klenerman (Cambridge)

Peter St George Hyslop (Cambridge)
Clemens and Gabi Kaminski (Cambridge)
Ellen Nollen (Groningen)
Ryan Limbocker (West Point)
Alfonso De Simone (Imperial College)
Gonçalo Bernardes (Cambridge)
Gian Gaetano Tartaglia (IIT)
Carlo Camilloni (Milan)
Max Bonomi (Pasteur)
Michael Zasloff (Enterin)
Monica Fuxreiter (Padova)