Genetics Core Update and ADNI-3 Plans

Andy Saykin, Indiana University

For the Genetics Core/Working Groups

ADNI Steering Committee, Washington DC
April 20, 2015
Genetics Core/Working Groups

Indiana University

• Imaging Genomics Lab
  – Andrew Saykin (Leader)
  – Li Shen (co-Leader)
  – Sungeun Kim
  – Kwangsik Nho
  – Shannon Risacher
  – Vijay Ramanan

• National Cell Repository for AD
  – Tatiana Foroud (co-Leader)
  – Kelley Faber

PPSB Working Group Members

– Xiaolan Hu (BMS)
– Enchi Liu (Janssen)
– Leanne Munsie (Lilly) *
– Qingqin Li (J&J)
– Nadeem Sarwar (Eisai) *
– Adam Schwarz (Lilly)
– Holly Soares (BMS)
– Dave Stone (Merck)
– FNIH Team

* Genetics Core Liaisons

Core Collaborators/Consultants

– Steven Potkin (UCI; co-Leader)
– Lars Bertram (Max Planck)
– Lindsay Farrer (BU)
– Robert Green (BWH)
– Matt Huentelman (TGen)
– Jason Moore (Dartmouth)
– Paul Thompson (USC)

Other Collaborators – RNA and NGS Projects:

– Liana Apostolova (UCLA)
– Nilufer Ertekin-Taner (Mayo Clinic)
– Keoni Kauwe (BYU)
– Yunlong Liu (Indiana)
– Fabio Macciardi (UC Irvine)

2014
Original ADNI-2 Specific Aims

*Progress Report & Impact*

Aim 1: Blood sample processing, genotyping and dissemination

Aim 2: Genome-wide analysis of multidimensional phenotypic data collected on the ADNI cohort

Aim 3: Serve as a central resource, point of contact and planning group for genetics in ADNI
Aim 1: Blood sample processing, genotyping and dissemination

• 1707 participants have at least 1 lymphoblastoid cell line (LCL) DNA sample banked at NCRAD*
  – 810 ADNI-1, 125 ADNI-GO, and 772 ADNI-2

• 1685 participants have at least 1 DNA sample from genomic blood extracted and banked*
  – 777 ADNI-1, 127 ADNI-GO, and 781 ADNI-2

• 1198 participants have RNA samples*
  – RNA collection was initiated in ADNI-GO
  – ADNI-1 subjects who continued to ADNI-GO/2 have RNA samples; 290 ADNI-1, 128 ADNI-GO, and 780 ADNI-2 subjects have at least 1 RNA sample stored at NCRAD

* Data as of 3/24/2015
Aim 1: Blood sample processing, genotyping and dissemination – cont’d

• Genotyping
  – All samples: APOE, DNA fingerprinting & GWAS (n=1724*)
  – Unique individuals with GWAS (n=1674) (8 more need QC repeat)
  – ADNI-1: TOMM40 PolyT (n=757)

• Genome-wide association studies (GWAS)
  – ADNI-1 Illumina 610 Quad (n=818*)
  – ADNI-GO/2 Illumina OmniExpress (n=793)
  – Illumina Omni2.5M (n=817*) – completed with WGS

• Whole exome sequencing (WES) – n=18 (extreme phenotype)
• Whole genome sequencing (WGS) – n=808 (Broad VCF set)
• RNA genome-wide expression profiling (Affymetrix array)
  – Pending QC: n~746 of 811 PaxGene blood RNA tubes (BMS)

* 1674/1724 GWAS available; local IRB related embargo: 61/818; 5/817; updated 4/2015
Requests for BAM files are served in the order received.

Total space needed for BAM files is ~96TB and requesters are required to provide their own hard drive.

The copying & validation process takes 3-4 weeks per copy.

We’ve received 27 requests to date and served 14:
- 20 Research
- 2 Pharmaceutical
- 4 Biotech
- 1 Gov
Aim 2: Genome-wide analysis of multidimensional phenotypic data collected on the ADNI cohort

ADNI Genetics Data Use and Reports (2008 to 2014)

Publications

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As of 1/1/2015

Shen et al, Brain Imaging Behav 2014; Yao et al, AAIC 2014 & AAIC 2015; Saykin et al, submitted
ADNI Genetics Data Use and Reports (2008 to 2014)

Journal Counts

Shen et al, Brain Imaging Behav 2014; Yao et al, AAIC 2014 & AAIC 2015; Saykin et al, submitted

As of 1/1/2015
ADNI Genetics Data Use and Reports (2008 to 2014)

Gene Counts

As of 1/1/2015

Shen et al, Brain Imaging Behav 2014; Yao et al, AAIC 2014 & AAIC 2015; Saykin et al, submitted
ADNI Genetics Data Use and Reports (2008 to 2014)

Gene Counts without APOE

As of 1/1/2015

Shen et al, Brain Imaging Behav 2014; Yao et al, AAIC 2014 & AAIC 2015; Saykin et al, submitted
Aim 2: Genome-wide analysis of multidimensional phenotypic data collected on the ADNI cohort

- ADNI APOE data has been reported extensively regarding MCI and AD
- ADNI GWAS data - Selected contributions highlighting impact

ADNI GWAS and related studies in MCI and AD:

- 2009: 1st GWAS of MRI hippocampal volume in AD
- 2010: 1st GWAS of CSF amyloid and tau markers
- 2010: 1st whole brain ROI-based GWAS & voxel-based GWAS
- 2010: 1st GWAS of longitudinal hippocampal MRI change
- 2010: Among 1st studies of mitochondrial DNA variations in AD
- 2011: Replication sample in very large-scale AD case-control GWAS
- 2011: Among the 1st reports of copy number variation (CNV) in AD/MCI
- 2012: Sample in two of the 1st large-scale genetic meta-analyses of MRI
- 2012: 1st gene pathway analysis of amyloid PET (PiB)
- 2012: Among the 1st gene pathway analyses of memory impairment
Aim 2: Genome wide analysis and impact of ADNI
MCI and AD phenotypes – continued

– 2013: 1st GWAS of amyloid PET (florbetapir)
– 2013: 1st MRI study of recently discovered TREM2 variant
– 2013: 1st whole-exome sequencing study in MCI (1st extreme MRI phenotype in MCI)
– 2013: Demonstrated strong influence of genetic variation on plasma protein levels
– 2013: 1st large scale WGS data set released to scientific community – analyses begin
– 2013: 1st GWAS of the healthy human structural connectome discovers SPON1 gene
– 2014: Largest GWAS of memory at the time - FASTKD2 gene discovered and associated with hippocampal structure on MRI
– 2014: Metabolomics collaboration launched (to include gene-metabolite studies)
– 2015: WES detects REST as novel neuroprotective target in MCI
– 2015: RNA baseline expression profiling and quality control nears completion
– 2015: Numerous discovery, replication & methods studies continue using ADNI data
Novel Target Discovery Examples

fas-activated serine/threonine kinase domains 2 (Chr 2q33.3)

FASTKD2 and human memory: functional pathways and prospects for novel therapeutic target development for Alzheimer’s disease and age-associated memory decline

“...the mechanisms underlying Alzheimer's disease and other age-related conditions causing cognitive deficits are only partially understood, limiting the development of disease-modifying therapies and novel early diagnostic biomarkers.”

Keywords: Alzheimer’s disease • apoptosis • cognitive aging • drug target • FASTKD2 • fas-associated serine/threonine kinase domains 2 • functional genomics • inflammation • memory • microRNA • mitochondria

Impairment in episodic memory is typically the earliest clinical deficit to appear in Alzheimer’s disease (AD), the most common cause of dementia and a source of immense personal and societal burden. Unfortunately, the mechanisms underlying AD and other age-related conditions causing cognitive deficits are only partially understood, limiting the development of disease-modifying therapies and novel early diagnostic biomarkers.

Recently, we reported the discovery of a SNP in the FASTKD2 gene associated with increased risk of cognitive impairment against AD and age-associated cognitive decline. As a result, this is an opportune moment to critically appraise extant knowledge about FASTKD2 and its functional pathways in order to guide next steps aimed at translating mechanistic knowledge into potential clinical strategies.

FASTKD protein family

FASTKD2 encodes one of a family of proteins (including FASTK and FASTKD1–5) that share a common structure including a unique cysteine-rich region in the N-terminal domain.
**ORIGINAL ARTICLE**

*FASTKD2* is associated with memory and hippocampal structure in older adults

VK Ramanan¹,²,³, K Nho¹, L Shen¹,⁴, SL Risacher¹, S Kim¹, BC McDonald¹,⁵,⁶, MR Farlow⁵,⁶, TM Foroud¹,²,⁴,⁶, S Gao⁶,⁷, H Soininen⁸,²⁸, I Kloszewska⁹, P Mecocci¹⁰, M Tsalaki¹¹, B Vellas¹², S Lovestone¹³, PS Aisen¹⁴, RC Petersen¹⁵, CR Jack Jr¹⁶, LM Shaw¹⁷,¹⁸, JQ Trojanowski¹⁷,¹⁸, MW Weiner¹⁹,²⁰, RC Green²¹, AW Toga²², PL De Jager²³,²⁴,²⁵, L Yu²⁶, DA Bennett²⁶, AJ Saykin¹,²,⁴,⁶ and for the Alzheimers Disease Neuroimaging Initiative (ADNI)²⁷

**Figure a**
- Rs7594645 (*FASTKD2*)
  - $p = 3.11 \times 10^{-9}$
  - Recombination rate (cM/Mb)

**Figure b**
- Immediate memory recall (10 word list)
  - Cohen’s $d = 0.42$
  - Cohen’s $d = 0.20$

**Cohorts:** HRS, ADNI-1, ADNI GO/2, AddNeuroMed, IMAS, ROS/MAP
Figure 3. Effect of FASTKD2 rs7594645-G on hippocampal volume and gray matter density in 315 older healthy control participants from the ADNI (Alzheimer’s Disease Neuroimaging Initiative). Using high-resolution T1-weighted structural magnetic resonance imaging (MRI), mean volumes and gray matter densities in the hippocampus (adjusted for age, gender, education and intracranial volume) ± s.e.s. are displayed based on rs7594645 genotype. Participants with the minor allele (G) of rs7594645 displayed increased hippocampal volume and gray matter density, with a significant multivariate effect of genotype on these MRI measures ($P = 0.036$).
FASTKD2 (fas-activated serine/threonine kinase domains 2)

• Highly expressed in the hippocampus throughout adulthood (Human Brain Transcriptome database)

• Mitochondrial regulator of apoptosis (Yeung et al., *Mol Cell Biol* 2011)

• Signaling through upstream activator Fas (“death receptor”)
  – Neuronal responses to traumatic brain injury (Beier et al., *Cell Res* 2007)
  – Amyloid-β-induced neurodegeneration (Su et al., *Neurobiol Dis* 2003)
  – Methamphetamine-induced neurodegeneration (Jayanthi et al., *PNAS* 2005)
  – Frontotemporal lobar dementia (Hu et al., *Neurology* 2010)

• Rare mutations associated with infantile encephalopathy due to electron transport chain complex IV deficiency (Ghezzi et al., *AJHG* 2008)

• rs7594645 resides in an intron overlapped by *MIR3130-1* and -2
  – Micro RNAs: small, non-coding RNAs → base-pair with complementary sequences in coding mRNAs to direct their degradation or translational repression
  – Genetic variation may alter mRNA-miRNA interactions to regulate FASTKD2 expression
REST: Protective Variant
Repressor element 1-silencing transcription factor (4q12)
Expressed in cortex & hippocampus, Represses genes involved in cell fate, cell death & neurogenesis, Role in protection against oxidative stress & amyloid toxicity

Lu et al Nature (2014)

REST and stress resistance in ageing and Alzheimer’s disease
Tao Lu1, Liu Arou1, Joseph Zuko1, Ying Pang2, Haoyoung Kim3, Ywen Chen2, Jun-Hsiang Yang2, Hyun-Min Kim4, Derek Drake5, X Shirley Liu2, David A. Bennett3, Monica P. Colacicco3 & Bruce A. Yankner1

Human neurons are functional over an entire lifetime, yet the mechanisms that preserve function and protect against neurodegeneration during ageing are unknown. Here we show that induction of the repressor element 1-silencing transcription factor (REST) in normal human cortical and hippocampal neurons is a universal feature of normal ageing in the mouse brain leads to age-related neurodegeneration. A functional orthologue of REST, Caenorhabditis elegans SPR-1, also protects against oxidative stress and amyloid β-protein toxicity and, is elevated in Alzheimer’s disease, frontotemporal dementia and dementia with Lewy bodies. REST is lost from the nucleus and appears in autophagosomes together with pathological misfolded proteins. Finally, REST levels during ageing are closely correlated with cognitive preservation and longevity. Thus, the activation state of REST may distinguish neuroprotection from neurodegeneration in the ageing brain.

We used whole genome sequencing to identify variants other than APOE associated with the rate of hippocampal atrophy in amnestic mild cognitive impairment. An in silico predicted missense variant in REST (rs2796559) was found exclusively in subjects with slow hippocampal volume loss and validated using unbiased whole brain analysis and meta-analysis across 5 independent cohorts. REST is a master regulator of neurogenesis and neuronal differentiation that has not been previously implicated in Alzheimer disease.

From the Center for Neuroimmunology, Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN; Center for Computational Biology and Bioinformatics, Indiana University School of Medicine, Indianapolis, IN; Neurogenetics Division, Translational Genomic Research Institute, Phoenix, AZ; Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN; Medical Scientist Training Program, Indiana University School of Medicine, Indianapolis, IN; Department of Mathematics, Rose Hamlin Institute of Technology, Terre Haute, IN; Department of Neurosciences, University of California, San Diego, San Diego, CA; Department of Genetics, University of British Columbia, Vancouver, BC, Canada; Division of Genetics, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA; Department of Radiology, Medicine, and Psychiatry, University of California, San Francisco, San Francisco, CA; Department of Veterans Affairs Medical Center, San Francisco, CA; Department of Medicine (Neurological Sciences), Brackenridge University School of Medicine, Houston, TX; Department of Biostatistics, School of Public Health, Boston, Boston, MA; Department of Neurology, University of California, San Francisco, San Francisco, CA; Institute of Psychiatry, Kings’ College London, London, United Kingdom; National Institute for Health Research Biomedical Research Centre for Mental Health, South London and Maudsley National Health Services Trust, Institute of Psychiatry, Kings’ College London, London, United Kingdom; Institute of Gerontology and Geriatrics, University of Hong Kong, Hong Kong, China; National Health Services Trust, Institute of Psychiatry, Kings’ College London, London, United Kingdom; Institute of Alzheimer’s Disease Research, National Institute on Aging, National Institute on Aging, National Institute of Health and Medical Research, Stockholm, Sweden; Department of Neurology, Massachusetts General Hospital, Harvard Medical School, National Institutes of Health, Bethesda, MD, USA; Department of Neurology, University of Edinburgh, Edinburgh, Scotland, UK; Department of Neurology, Indiana University School of Medicine, Indianapolis, IN; and Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN

Address correspondence to Dr. Saykin, Center for Neuroimmunology, Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN 46202. E-mail: saykin@iu.edu

Date used in preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (dclinica.scripps.edu). As such the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or preparation of this report. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/content/uploads/howtoapply/ADNI_Acknowledgement_List.pdf.

Received Nov 1, 2014; Revised Dec 15, 2014; Accepted for publication Dec 30, 2014.

View this article online at WIREsNeuroImmunol.com. DOI: 10.1002/wneu.201400155

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Nho et al Annals of Neurology 77(3); 2015
Exome Sequencing - Protective Effects: REST
Repressor element 1-silencing transcription factor
Investigation in ADNI-1 (n=315)

Quantitative Trait Loci (QTL) analysis and surface-based analysis

<table>
<thead>
<tr>
<th></th>
<th>All APOE ε3/ε3 (N=315)</th>
<th>APOE ε3/ε3 MCI (N=135)</th>
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<tr>
<td>Volume</td>
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</tr>
<tr>
<td>APC</td>
<td>0.8964</td>
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<tr>
<td>Slope</td>
<td>0.6568</td>
<td>0.7524</td>
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<td><strong>Left Hippocampus</strong></td>
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<tr>
<td>Volume</td>
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<td><strong>Mean Hippocampus</strong></td>
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<td>Slope</td>
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<td>0.9110</td>
</tr>
</tbody>
</table>

Effect of rs3796529 on hippocampal volume at baseline (Cross-sectional)

Effect of rs3796529 on cortical thickness at baseline (Cross-sectional)

Subjects with minor alleles of rs3796529 showed larger hippocampal volume and cortical thickness in the temporal lobe regions

REST: Meta-Analysis
5 Independent Cohorts (N=923)

Quantitative Trait loci (QTL) Association Analysis using hippocampal volume as endophenotypes

rs3796529 (REST)

<table>
<thead>
<tr>
<th>Studies</th>
<th>Standardized Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADNI-1</td>
<td>-0.287 (-0.525, -0.049)</td>
</tr>
<tr>
<td>ADNI-GO-2</td>
<td>-0.089 (-0.383, 0.204)</td>
</tr>
<tr>
<td>IMAS</td>
<td>-0.045 (-0.739, 0.649)</td>
</tr>
<tr>
<td>AddNeuroMed</td>
<td>-0.028 (-0.389, 0.333)</td>
</tr>
<tr>
<td>MIRAGE</td>
<td>-0.142 (-0.418, 0.134)</td>
</tr>
<tr>
<td>Overall</td>
<td>-0.159 (-0.297, -0.020)</td>
</tr>
</tbody>
</table>

\[ P = 0.02 \]

Effect of rs3796529 on right hippocampal volume at baseline

Subjects with minor alleles of rs3796529 showed larger hippocampal volume


*Cohorts: ADNI-1, ADNI-GO/2, IMAS, AddNeuroMed, MIRAGE*
ADNI 3 – OVERALL SPECIFIC AIMS

*Genetics can contribute to each goal*

**Overall goal:** validation of biomarkers for AD

- **Longitudinal change of cognition and biomarkers:** measures that capture longitudinal change with highest statistical power
- **Prediction of cognitive decline:**
- **Clinical trial design:** Optimum outcome measures, predictors, and inclusion/exclusion criteria for clinical trials
- **Discovery:** new markers, new targets
Genetics Aims for ADNI-3

Overview

• Aim 1: Data collection, sample banking, quality control and dissemination

• Aim 2: Comprehensive and integrative genomics and bioinformatics analysis

• Aim 3: Determine the clinical and biological significance of identified variants

• Aim 4: Continue to provide organization, collaboration and leadership for genomic studies of quantitative biomarker phenotypes
Scientific Rationale & Hypotheses

• Genetics informs precision medicine and impacts trial design
  – Examples: A4, API Columbian kindred and APOE, DIAN-TU, TOMMORROW Study
  – Understand disease heterogeneity – phenotype profile, rate of progression
    • Analyses in current samples, eg, amyloid vs tau vs inflammatory subtypes – treatable subsets?
    • Role of gene pathways & networks in comorbidities – “diseasome”
    • Existing Pharma data sets have relatively little longitudinal follow-up and usually incomplete biomarker panels

• Discovery, validation and prioritization of diagnostic and therapeutic targets
  – Current: APOE, TOMM40, BCHE (rivastigmine, now amyloid), TREM2 .... Promising nominations: FASKD2, REST
  – Future: prescription by genotype with PGX screen to avoid adverse effects
Genetics Core ADNI-3 Specific Aims

• **Aim 1: Data collection, sample banking, quality control and dissemination**
  – Serial DNA and RNA collection for genomic, transcriptome and epigenetic studies
  – Extend current collection to include fibroblasts and PBMCs for development of induced pluripotent stem cells (iPSCs)

• **Aim 2: Comprehensive and integrative genomics and bioinformatics analysis**
  – Complete *APOE*, GWAS, DNA and RNA sequencing and epigenetic analyses (quality control and organize for user-friendly dissemination)
  – Identify variants that improve prediction of genetic risk & modulate AD biomarker curves
  – Identify baseline variants that enhance clinical trial design through risk enrichment and stratification based on genetic subtyping
  – Identify dynamic changes associated with disease progression (transcriptome, epigenetic markers)
  – Identify gene networks and pathways associated with risk, phenotypic profiles and progression through systems biology
Genetics Core Specific Aims – Cont’d

• **Aim 3: Determine the clinical and biological significance of identified variants**
  - Family studies of ADNI participants enriched for LOAD (FH+) or carrying informative risk or protective variants; e.g. FH+/ε4- cases to identify other risk genes; ε4+/FH- controls to discover potential protective variants; Collaborate with the Clinical Core for follow-up and family recruitment
  - Replication studies using other family-based and case-control cohort data sets
  - Functional genomic follow-up studies – collaborate with industry and academic partners for therapeutic target identification and characterization of mechanism
  - Collaborate with Neuropathology Core - relate blood and brain RNA expression

• **Aim 4: Continue to provide organization, collaboration and leadership for genomic studies of quantitative biomarker phenotypes**
  - Cores/sites within ADNI, industry & academic partners; 3 working groups
  - Foster collaboration with ADGC/ADSP, DIAN, WW-ADNI cohorts and other national/international consortia, AD prevention trials and RNA & iPSC groups
Converging -omics & Systems Biology

Molecular Networks/Pathways

Transcriptome**: RNA sequence and expression
Proteome*: Protein expression, structure, and function
Metabolome*: Metabolite / enzyme profile
Epigenome†: DNA methylation and histone modification
Interactome†: Interaction (e.g., gene-gene, gene-protein)
Genome**: DNA sequence and variation
Exposome**: Environment, life style, diet, drug, age
Brain structure & function**: Structural and functional brain imaging
Connectome**: Anatomical and functional brain connectivity

Perturbed biochemical networks/pathways

Healthy vs Disordered Brains†

Healthy Brain + AD Brain
Healthy Brain + AD Brain

Structure
PiB PET
Function
Connectivity

Systems Biology Approach

Sungeun Kim et al; Adapted from Ramanan & Saykin, Pathways to Neurodegeneration, AJND (2013) 2(3):145-175
Systems Biology Working Group

• Genetics Core (IU, UCI, USC)
• PPSB Core Liaisons & other company experts
  – Biogen, Eisai, Eli Lilly (others welcome)
• EAC Representatives
• Metabolomics Network (Duke University)
• Sage Bionetworks
• Orion Bionetwork
• In-Silico Biosciences
• AMP-AD Investigators
• Other academic labs (Emory, MSSM, Penn, Rush)
Path from genetic signal to targeted therapeutics: key applications to drug discovery and development

Discover loci/genes robustly associated with relevant trait
- Common variant associations
- Rare variant associations
- Monogenic disorders
- Family-based

Identify causal gene underpinning pathogenesis
- Mapping / Sequencing
- Tissue expression
- eQTL, pQTL, mQTL
- Pathway analysis

Understand biological pathway
- Gene-centric phenome scans
- iPSC and related
- In-vitro functional assessment
- Gene editing

Understand underlying mechanism

Identify biomarkers
- Molecular pharmacology
- Assay development
- Cell-based perturbation
- Mechanistic models

Develop therapeutic hypothesis

Identify patients most likely to benefit
- Biomarker development
- Molecular epidemiology
- Clinical trial samples
- Clinical imaging

Target discovery and qualification

Understanding disease biology

Stratification & enrichment

Nadeem Sarwar, Eisai