Translational Medicine: Pathways to Discovery and Implementation

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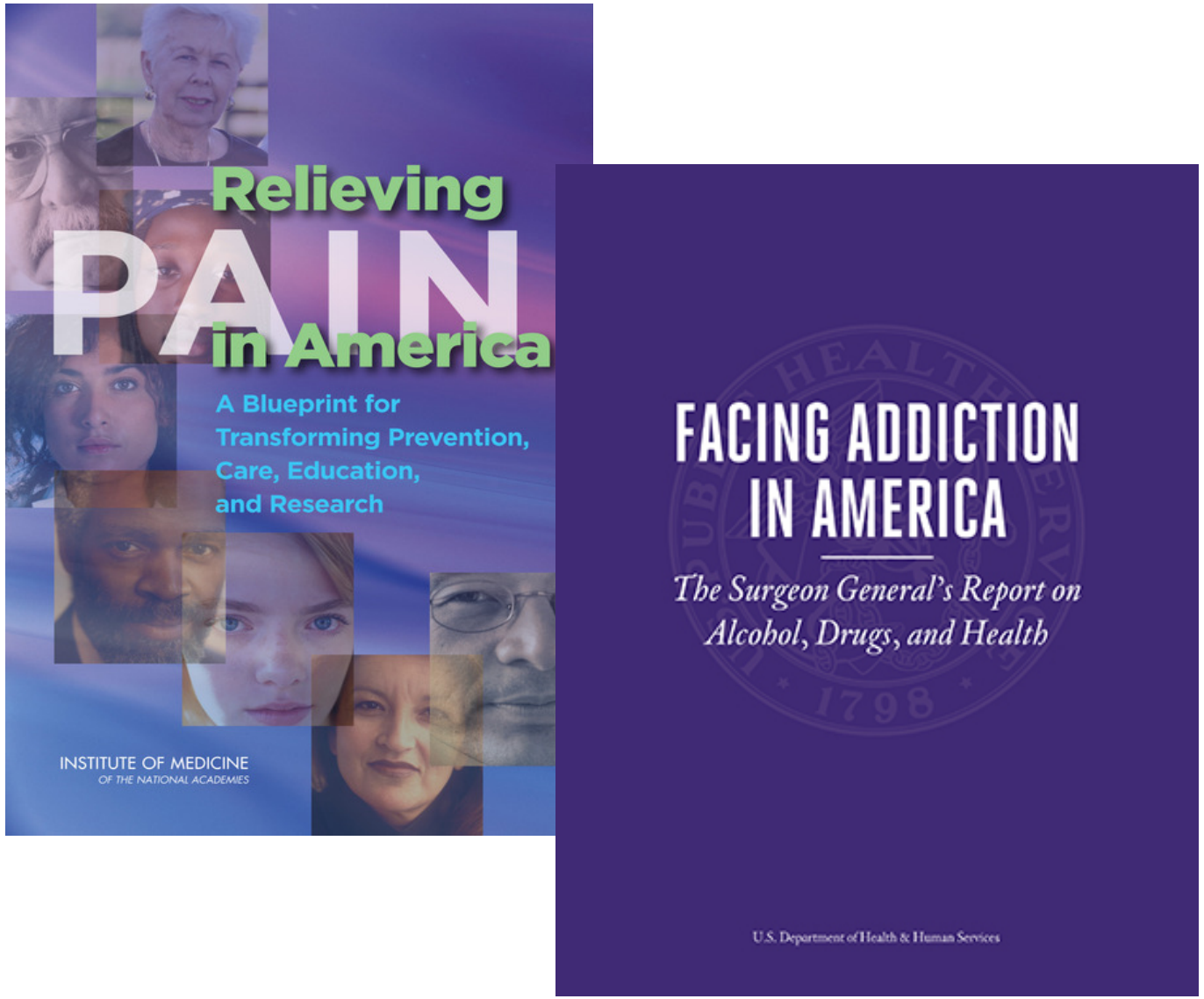
Disclosures: Algynomics Inc. cofounder and equity shareholder; ATTAGENE Inc shareholder; Orthogen Inc. equity shareholder and BoD

Interwoven Epidemics: With a Common Solution
Discovery and Development of Non-Opioid Therapies



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Center for Translational Pain Medicine - Duke

UNC School of Dentistry

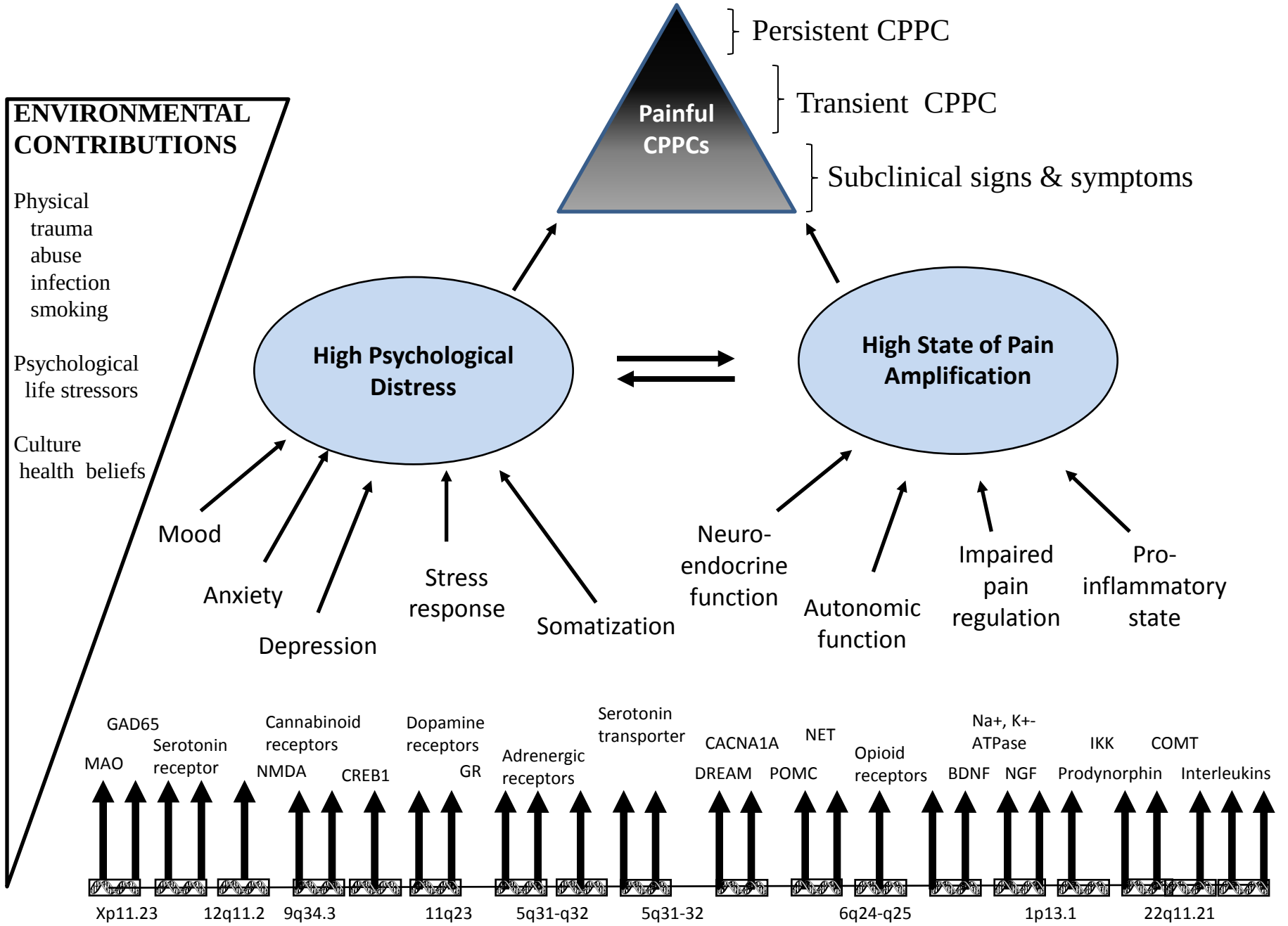
Thurston Arthritis Center

Attagene Inc.

Algynomics Inc.

A Guiding Principle

Most acute and chronic pain conditions are manifested as a kaleidoscope of phenotypes that are temporally dynamic and result from GxE interactions



Diatchenko et al, Pain 123: 226-30, 2006 & Maixner et al, Journal of Pain 12, Suppl 3, 4-11, 2011

Research Paper

PAIN

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Identification of clusters of individuals relevant to temporomandibular disorders and other chronic pain conditions: the OPPERA study

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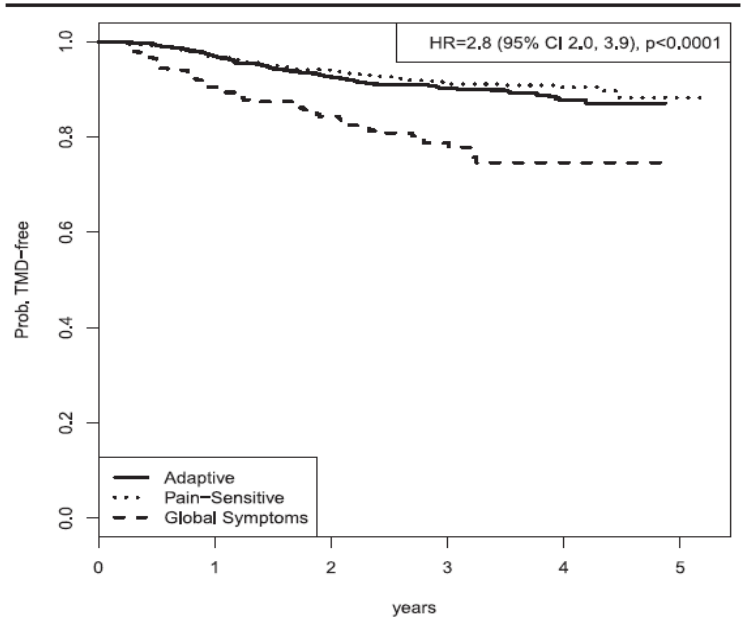
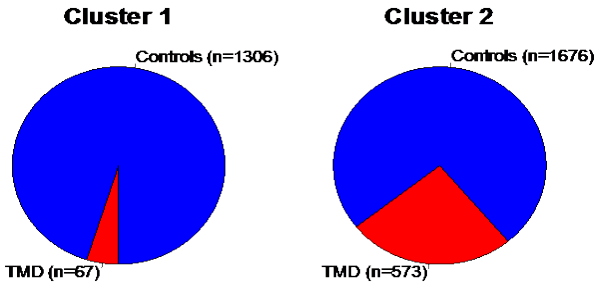
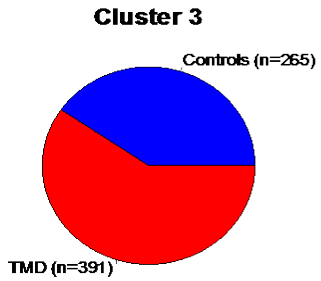
Abstract

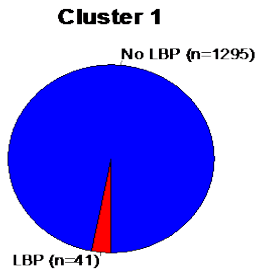
The classification of most chronic pain disorders gives emphasis to anatomical location of the pain to distinguish one disorder from the other (eg, back pain vs temporomandibular disorder [TMD]) or to define subtypes (eg, TMD myalgia vs arthralgia). However, anatomical criteria overlook etiology, potentially hampering treatment decisions. This study identified clusters of individuals using a comprehensive array of biopsychosocial measures. Data were collected from a case–control study of 1031 chronic TMD cases and 3247 TMD-free controls. Three subgroups were identified using supervised cluster analysis (referred to as the adaptive, pain-sensitive, and global symptoms clusters). Compared with the adaptive cluster, participants in the pain-sensitive cluster showed heightened sensitivity to experimental pain, and participants in the global symptoms cluster showed both greater pain sensitivity and greater psychological distress. Cluster membership was strongly associated with chronic TMD: 91.5% of TMD cases belonged to the pain-sensitive and global symptoms clusters, whereas 41.2% of controls belonged to the adaptive cluster. Temporomandibular disorder cases in the pain-sensitive and global symptoms clusters also showed greater pain intensity, jaw functional limitation, and more comorbid pain conditions. Similar results were obtained when the same methodology was applied to a smaller case–control study consisting of 199 chronic TMD cases and 201 TMD-free controls. During a median 3-year follow-up period of TMD-free individuals, participants in the global symptoms cluster had greater risk of developing first-onset TMD (hazard ratio = 2.8) compared with participants in the other 2 clusters. Cross-cohort predictive modeling was used to demonstrate the reliability of the clusters.

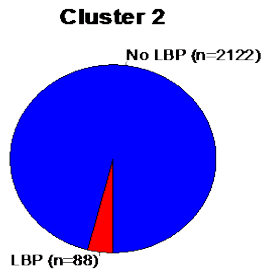
Keywords: Temporomandibular disorders, Clustering, Classification of chronic pain

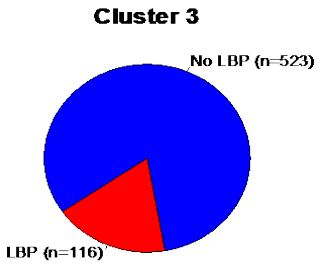


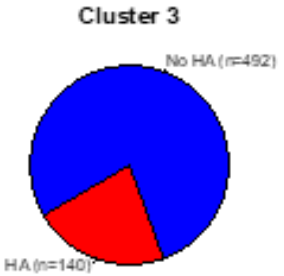




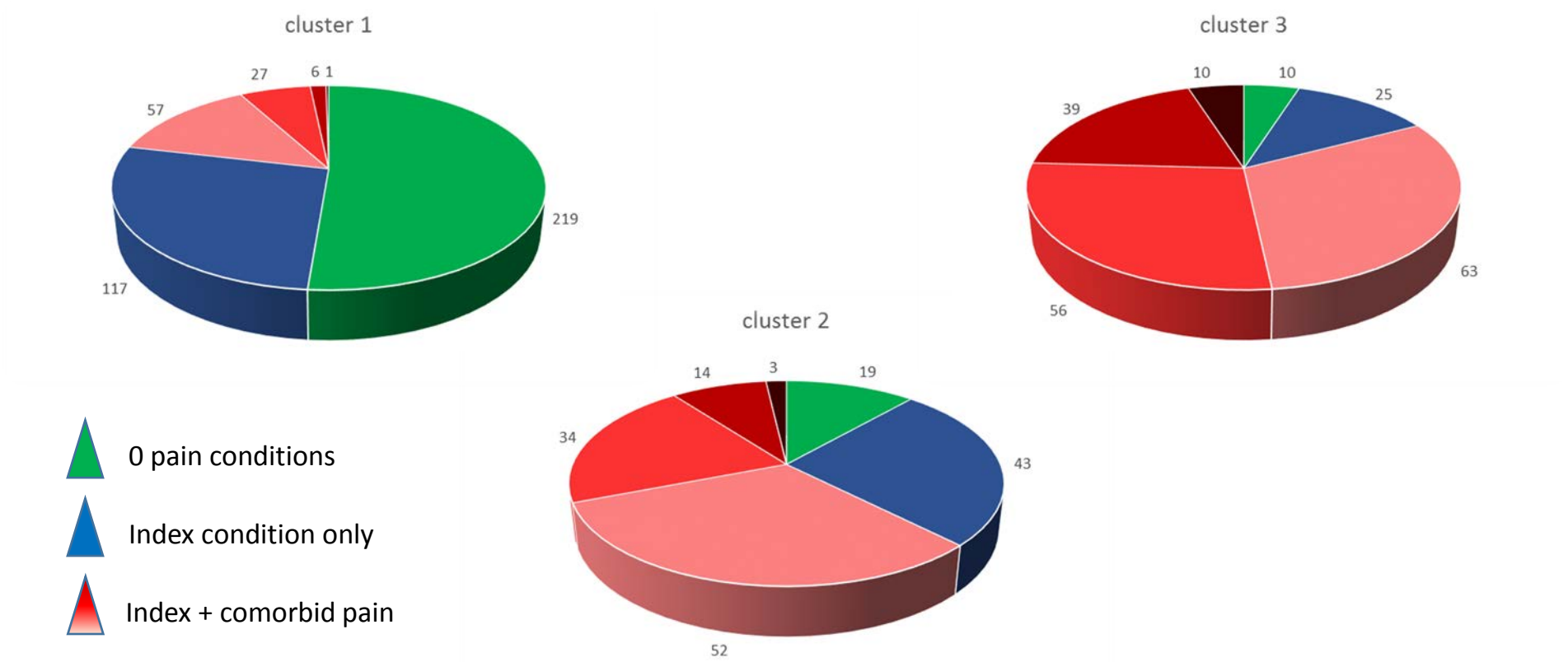








Preliminary Findings - Comorbidities by Cluster



Epiregulin and EGFR interactions are involved in pain processing

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Differences in the Antinociceptive Effects and Binding Properties of Propranolol and Bupranolol Enantiomers

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Expansion of the human μ-opioid receptor gene architecture: novel functional variants

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6TM – Opioid Program: Activities

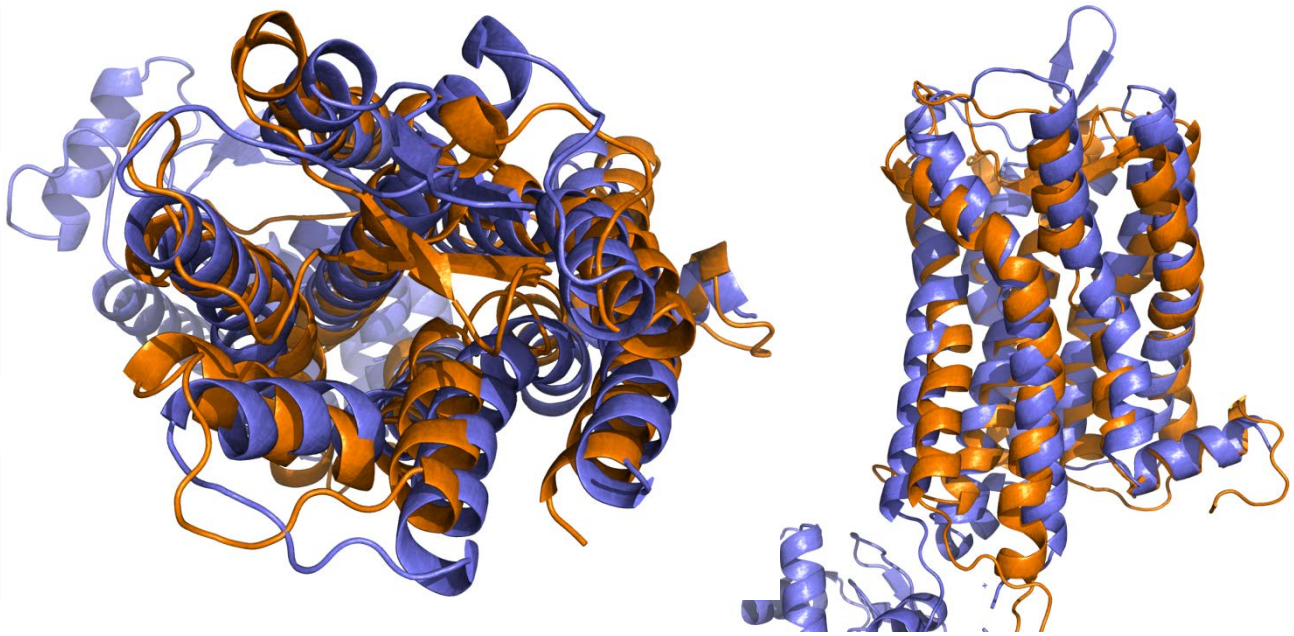
Structural models of 6TM and 7TM

Validate models in experiments

Perform virtual screening

Test best-scoring hits in cellular assays

Test best performing hits in animals → leads



RMSD = 3.5 Å

Serohijos et al., *Structure*, 19: 1683-1690 (2011)

Manglik et al., *Nature,* in press (2012)

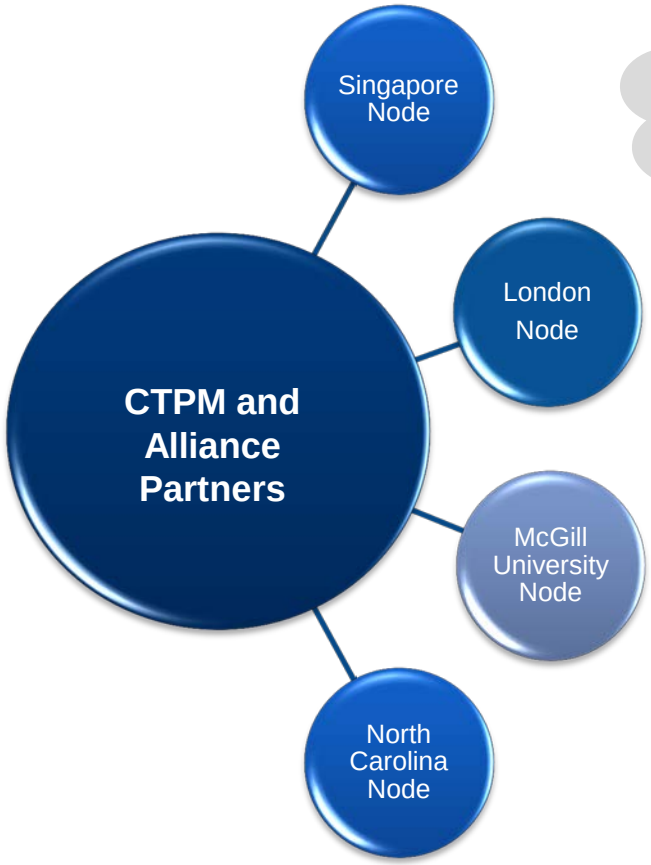
A few putative targets identified (reverse translation) or confirmed (forward translation) by human genetic studies

- COMT/ β_2
  - Completed POC
  - NCEs under development
- Novel opioid receptor splice variants (eg. OPRM1/OPRM1-β_2)
  - NCE under development
- EGFR and associated downstream pathways
- Nicotinic receptors
- α2δ2 calcium channel subunit
- CA8
- KCNS1
- CGH1
- SCN9A/Nav1.7
- P2X7 receptor
- 5HT2a

Aims of a Public-Private Consortium

- To collect and integrate data from large human cohorts
- To develop new bioinformatic tools for target discovery
- To conduct mechanistic animal and cellular studies
- To develop a clinical trials network of public/private stakeholders

Pain Management/Pain Research Module



Center for Translational Pain Medicine

- ✓ Secure cloud system
- ✓ HIPAA compliant
- ✓ Customizable & scalable
- ✓ Core Phenotypes:
  - ❑ Medical
  - ❑ Pain
  - ❑ Symptoms
  - ❑ Coping
  - ❑ Stress
  - ❑ Sleep
  - ❑ Risk factors
  - ❑ Satisfaction
- ✓ Biologics
- ✓ LabVantage LIMS
- ✓ PEDIGENE linkage
- ✓ Reports and Analyses
- ✓ EPIC DataMart linkage