Where are we in Narcolepsy and Hypersomnia research?

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History of Narcolepsy

- 1877 — Syndrome first described
- 1918 — Von Economo’s *Encephalitis Lethargica*
- 1930 — Stimulant treatments
- 1959 — Sleep-onset REM periods at night
- 1979 — MSLT and cases without cataplexy
  - Idiopathic hypersomnia versus narcolepsy without cataplexy
- 1983 — Association with immune related human leukocyte antigens (HLA) in 95% with cataplexy
- 2000s — Cloning of canine narcolepsy gene and implication of low hypocretin
  - ~95% with cataplexy (T1) vs 15% without cataplexy (T2)
- 2010s — Autoimmune basis of narcolepsy and role of influenza A in T1 narcolepsy
- 2015 — What is T2 narcolepsy and Idiopathic hypersomnia
Human narcolepsy-cataplexy

- Excessive daytime sleepiness
- Cataplexy
- Sleep paralysis
- Hypnagogic hallucinations
- Disturbed sleep
- Sleep Onset REM periods

Prevalence approximately 0.05% with cataplexy
Sporadic disorder, rarely familial but increased risk in family members
onset most commonly during adolescence

Courtesy, Giuseppe Plazzi

Westphal (1877); Gelineau (1878)
Unlike in humans, many canine narcolepsy cases are genetically transmitted as a single gene.

10 years >>>>Single gene and Direct transitions to REM sleep paralysis

(video) Narcoleptic dog
Asymptomatic carrier dog
Hypocretin receptor (Hcrtr2) Mutations in genetic forms of narcolepsy in canines
Likely autoimmunity target: hypocretin

Control

1 cm

Narcoleptic

1 cm

mRNA in situ Hybridization

CSF Hypocretin-1

Hypocretin

MCH

Narcoleptic

Control

Peyron et al., 2000; Mignot et al., 2002; Scammell et al., 2004

Randomly selected case study
Nine questions in narcolepsy

• What is the genetic predisposition?
• How do these genes predispose to narcolepsy?
• What is/are the environmental factors involved?
• What aspects of the immune system is involved in hypocretin cell death?
• What is (are) the autoantigen (s)
• How can we diagnose faster and better?
  – Biochemical/immunological
  – Single night PSG plus genetics
• What is the true spectrum of the disease in the population?
• Can we prevent narcolepsy?
• Can we treat it better or even cure it?
More genetics: Genome Wide Association Studies (GWAS)

Single Nucleotide Polymorphisms (SNPs) covering all human chromosomes at high density

G/A (75%/25%)

Cases (narcolepsy)

G/A (70%/30%)

Controls (general population)
GWAS data support autoimmune hypothesis

111,240 SNP markers (HLA excluded)
High quality SNPs, >1% MAF, HLA excluded
Line indicates $-\log_{10} P = 4.49 \times 10^{-7}$ (Bonferroni)
T cell receptor implicates T cells

No detectable autoantibodies against hypocretin cells

Immunofluorescence using human serum and secondary anti human immunoglobulin

Systematic Isolation and autantibody testing of proteins coexpressed with hypocretin

islet cell staining with type I diabetes serum

Scatterplot comparing HCRT and Total Hypothalamus RNA as obtained using the BAC TRAP (hct:RB-P10) technology.

Autoimmunity difficult to detect or no B cell involvement
Immune pathways in narcolepsy involves T cells

Cytokines such as INF-\(\gamma\), TNF-\(\alpha\), IL2, IL17 & others

Virally infected cells

Hypocretin neurons

CD8 cells

TCR

HLA Class I

P2YR11

Antigen Presenting Dendritic cells

CD4 cells

TCR

HLA- Class II

INFAR1

CTSH

TNFSF4

Normal Antigen= piece of virus
Autoantigen= piece of hypocretin neuron
Seasonality and pH1N1: Identification of one trigger

A

B

C

Seasonal fluctuation of onset (all)

Onset (481)

Diagnosis (526)

Birth (526)

SPRING

SUMMER

WINTER

%
Pandemrix Vaccination Narcolepsy cases

**Sweden Data** (Szőkácz)
- OR=4.19 (1.76-12.1), children
- OR=1.21 (0.67-2.17), adults
(Based on LÄKEMEDELSVERKET Medical Products Agency Study March 28 2011)

**Finland Data** (Nohytek, Partinen)
- Coverage: 51.6% (75% 5-20)
- OR=12.7 (6.1-30.8) children

**France Data** (Dauvilliers)
- Coverage: 8.8%
- OR=6.5 (2.5-19.9) children
- OR=4.7 (6.5-13.9) adults

**Ireland Data** (Miller)
- Coverage: 22% (39% 5-19)
- OR=13.0 (4.8-44.7), children
- OR=18.8 (1.7-207.4), adults
(National Narcolepsy study Steering committee, April 19 2012)

**England Data** (O'Flanagan)
- Coverage: 15%
- OR=16.2 (3.1-84.5), children
(Miller et al., BMJ. 2013 Feb 26;346:f794)

Squalene/alpha-tocopherol (AS03)-based vaccine with A H1N1/CA/07/2009
## Association in vaccination related cases

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<th>A1</th>
<th>A2</th>
<th>N</th>
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<td>0.999</td>
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^aProxy for association was used rs4787458 instead of rs200840505 D' 0.98 r2 0.95

The direction resembles the association direction of A1 (effect) allele across three cohorts.
CD8 involvement in narcolepsy

CD8 T cell-mediated killing of orexinergic neurons induces a narcolepsy-like phenotype in mice

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Valnet et al, PNAS 2016 although it is an artificial model

What is the antigen remains unknown
**PERIPHERAL RESPONSE**

- CD4+ T-cell
- CD8+ T-cell
- Flu infected cell
- Release of Perforin and Granzyme

**CNS RESPONSE**

- CD4+ T-cell
- CD8+ T-cell
- Flu infected cell
- Release of Perforin and Granzyme

**Aim 1**

- Identify Pandemrix specific antigens

**Aim 2**

- Identify Pandemrix DQ0602 restricted CD4+ T-cells

**Aim 3**

- Identify mimic/auto antigens

**Aim 4**

- Identify auto specific CD8+ T-cells
Creation of reassortant vaccine strains

Hemagglutinin (pandemic 2009 H1)
Neuraminidase (pandemic 2009 N1)
Nucleoprotein (Pandemic 2009)

(PR8-A/H1N1/California/7/2009)

Ultra centrifugation to isolate HA, NA and viral components

Denaturation, solubilization using deoxycholate and filtration

Vaccines then packaged and dosed

Reassortant egg adapted PR8-A/H1N1/California/7/2009 propagated

Reassortant PR8 backbone with pdm H1 and N1

Nucleoprotein (PR8 Strain)
Reassortant strain mutations differ across vaccines

<table>
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<tr>
<th>Protein</th>
<th>Position</th>
<th>Aminoacid Mutation</th>
<th>2009 H1N1 Aminoacid</th>
<th>Region</th>
<th>Nucleotide mutation</th>
<th>HLA-DQB1*06:02 binding</th>
<th>Pandemrix&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Arepanrix</th>
<th>Focetria</th>
<th>Ratio Pandemrix/ Arepanrix</th>
<th>Ratio Pandemrix/ Focetria</th>
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<td>15.8% (127,806)</td>
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<td>1.11 1.91</td>
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<td>24.5% (53,216)</td>
<td>23% (185,806)</td>
<td>24.1% (20,83)</td>
<td>1.07 1.02</td>
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<td>25.3% (21,83)</td>
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<td>17.1% (37,216)</td>
<td>18% (145,806)</td>
<td>26.5% (22,83)</td>
<td>0.95 0.65</td>
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<td>A &gt; G</td>
<td>NA</td>
<td>9.3% (20,216)</td>
<td>10.4% (84,806)</td>
<td>12% (10,83)</td>
<td>0.89 0.78</td>
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<td>N</td>
<td>QMYTPGEVRNDDVDQSLIIA</td>
<td>A &gt; G</td>
<td>NA</td>
<td>33.3% (1,3)</td>
<td>58.3% (7,12)</td>
<td>NaN (0, 0)</td>
<td>0.57 NaN</td>
<td>0.57 NaN</td>
</tr>
</tbody>
</table>

* = Amhed et al. mutation
† = also found in Majid et al., Plos one 2015.

Jacob et al, in preparation
Confirmed for HA
Identifying T cells binding specific antigens using DQ0602-flu peptide-tetramers
Searching for the elusive T cell biomarker
Example of tetramer sorted single cell TCR sequencing (list of clones observed at least 7 times)

<table>
<thead>
<tr>
<th>Pep</th>
<th>Diagnosis</th>
<th>TRBV</th>
<th>CDR3β</th>
<th>TRBJ</th>
<th>TRAV</th>
<th>CDR3α</th>
<th>TRAJ</th>
<th>Clones</th>
<th>Note</th>
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<tbody>
<tr>
<td>NP23</td>
<td>P (15687)</td>
<td>6-2</td>
<td>CASGDYGTYTF</td>
<td>1-2</td>
<td>19</td>
<td>CALSEAGSLAGTASKLTF</td>
<td>44</td>
<td>15</td>
<td>S</td>
</tr>
<tr>
<td>NP136</td>
<td>P (16022)</td>
<td>4-2</td>
<td>CASSERGEAADT QYF</td>
<td>2-3</td>
<td>2</td>
<td>CAVAGTGANNLFF</td>
<td>36</td>
<td>57</td>
<td>S</td>
</tr>
<tr>
<td>NP136</td>
<td>P (15900)</td>
<td>4-2</td>
<td>CASSQERGSYNE QFF</td>
<td>2-1</td>
<td>12-2</td>
<td>CALGSARQLTFT</td>
<td>22</td>
<td>15(7)</td>
<td>S/D</td>
</tr>
<tr>
<td>NP136</td>
<td>C (15688)</td>
<td>4-2</td>
<td>CASSQGGAGGLGTDTQYF</td>
<td>2-3</td>
<td>2</td>
<td>CAVDRYGNKLVF</td>
<td>47</td>
<td>27</td>
<td>S</td>
</tr>
<tr>
<td>NP136</td>
<td>C (15901)</td>
<td>27</td>
<td>CASTPGQDGYT</td>
<td>1-2</td>
<td>12-1</td>
<td>CVVRGGSGGYIPTF</td>
<td>6</td>
<td>9</td>
<td>S</td>
</tr>
<tr>
<td>NP136</td>
<td>EO (15165)</td>
<td>20-1</td>
<td>CSAITIGSSYEQYF</td>
<td>2-7</td>
<td>38-2/DV8</td>
<td>CAYRSAIFDDKIIF</td>
<td>30</td>
<td>11</td>
<td>S</td>
</tr>
<tr>
<td>NP136</td>
<td>EO (15165)</td>
<td>20-1</td>
<td>CSAMVRGVSQT QYF</td>
<td>2-5</td>
<td>38-2/DV8</td>
<td>CAYRSALFGNEKLTFT</td>
<td>48</td>
<td>18</td>
<td>S</td>
</tr>
<tr>
<td>NP136</td>
<td>EO (15165)</td>
<td>20-1</td>
<td>CSASPQQLSTGE LFF</td>
<td>2-2</td>
<td>12-2</td>
<td>CAVTYFGGQFYF</td>
<td>49</td>
<td>18</td>
<td>S</td>
</tr>
<tr>
<td>NP136</td>
<td>EO (15165)</td>
<td>20-1</td>
<td>CSASSMGTSQPP QHF</td>
<td>1-5</td>
<td>12-2</td>
<td>CAVTYLGKLIF</td>
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<td>30</td>
<td>S</td>
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<td>P (16022)</td>
<td>20-1</td>
<td>CSPLLQGVVSTEAAFF</td>
<td>1-1</td>
<td>38-2/DV8</td>
<td>CAYRSPIFGNEKLTFT</td>
<td>48</td>
<td>18</td>
<td>S</td>
</tr>
</tbody>
</table>
Improved PSG analytics: Machine learning Convolutional Neural Network (ConvNet)

- A supervised prediction model in which the input data is low-level e.g. an image or a spectrogram.
- Features are constructed through a network of filter and subsampling layers.
- Deeper networks may construct more complex features.
- Resulting features depend on input data, as parameters change iteratively during training.
- Often used in computer vision or speech recognition tasks.

Example borrowed from: http://www.computervisionblog.com/2015/03/deep-learning-vs-machine-learning-vs.html

Example borrowed from: http://cs231n.github.io/convolutional-networks/
Machine Learning

- Feed-forward neural network (FFNN):
  - Process each observation independently

- Recurrent neural network (RNN):
  - Introduces a temporal dimension
  - Used to model change in frequency

- Long Short-Term Memory (LSTM) network
  - Introduces support for long-term dependencies
  - Context-aware decisions
### Type 1 - Net #1

<table>
<thead>
<tr>
<th>Layer Type</th>
<th>Output Shape</th>
<th>Input Shape</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conv 7x7 / 64</td>
<td>200x60x3xN</td>
<td>200x60x3xN</td>
</tr>
<tr>
<td>Max Pool 3x3 / 2</td>
<td>66x60x10x4xN</td>
<td>200x60x3xN</td>
</tr>
<tr>
<td>Conv 5x5</td>
<td>100x30x6x4xN</td>
<td>60x60x3xN</td>
</tr>
<tr>
<td>Avg Pool 24x7</td>
<td>1x1x256xN</td>
<td>1x1x256xN</td>
</tr>
<tr>
<td>Concatenate</td>
<td>1x1x576xN</td>
<td></td>
</tr>
<tr>
<td>Fully connected</td>
<td>1x1x512xN</td>
<td></td>
</tr>
<tr>
<td>Softmax output</td>
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</tr>
</tbody>
</table>

**Total nr. of parameters:** 
-2.8M

### Type 1 - Net #2

<table>
<thead>
<tr>
<th>Layer Type</th>
<th>Output Shape</th>
<th>Input Shape</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conv 7x7 / 64</td>
<td>200x60x3xN</td>
<td>200x60x3xN</td>
</tr>
<tr>
<td>Max Pool 3x3 / 2</td>
<td>66x60x10x4xN</td>
<td>200x60x3xN</td>
</tr>
<tr>
<td>Conv 5x5</td>
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<td>60x60x3xN</td>
</tr>
<tr>
<td>Avg Pool 24x7</td>
<td>1x1x256xN</td>
<td>1x1x256xN</td>
</tr>
<tr>
<td>Concatenate</td>
<td>1x1x576xN</td>
<td></td>
</tr>
<tr>
<td>Fully connected</td>
<td>1x1x512xN</td>
<td></td>
</tr>
<tr>
<td>Softmax output</td>
<td>1x1x512xN</td>
<td></td>
</tr>
</tbody>
</table>

**Total nr. of parameters:** 
-2.8M

### Type 2 - Net #3

<table>
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<tr>
<th>Layer Type</th>
<th>Output Shape</th>
<th>Input Shape</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conv 7x7 / 64</td>
<td>200x60x3xN</td>
<td>200x60x3xN</td>
</tr>
<tr>
<td>Max Pool 3x3 / 2</td>
<td>66x60x10x4xN</td>
<td>200x60x3xN</td>
</tr>
<tr>
<td>Conv 5x5</td>
<td>100x30x6x4xN</td>
<td>60x60x3xN</td>
</tr>
<tr>
<td>Avg Pool 24x7</td>
<td>1x1x256xN</td>
<td>1x1x256xN</td>
</tr>
<tr>
<td>Concatenate</td>
<td>1x1x576xN</td>
<td></td>
</tr>
<tr>
<td>Fully connected</td>
<td>1x1x512xN</td>
<td></td>
</tr>
<tr>
<td>Softmax output</td>
<td>1x1x512xN</td>
<td></td>
</tr>
</tbody>
</table>

**Total nr. of parameters:** 
-2.8M
Description of the 8 top narcolepsy features selected by lasso

<table>
<thead>
<tr>
<th>Number</th>
<th>Relative selection frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>The time taken before 5% of the sum of the product between W, N2 and REM, calculated at every epoch, has accumulated, weighed by the total amount of this sum. This feature expresses the known sleep stage dissociation and altered sleep timing.</td>
</tr>
<tr>
<td>2</td>
<td>0.91</td>
<td>The number of nightly SOREMPs appearing throughout the recording.</td>
</tr>
<tr>
<td>3</td>
<td>0.82</td>
<td>The time taken before 50% of the wakefulness in a recording has accumulated, weighed by the total amount of wakefulness.</td>
</tr>
<tr>
<td>4</td>
<td>0.82</td>
<td>REM 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The Shannon entropy of the REM sleep stage distribution. This expresses the amount of information held in a signal, or in this case, how many different values the REM sleep stage distribution obtains - how consolidated phases of REM are when the stage appears.</td>
</tr>
<tr>
<td>5</td>
<td>0.68</td>
<td>The maximum probability of wakefulness obtained in a recording.</td>
</tr>
<tr>
<td>6</td>
<td>0.68</td>
<td>The maximum value obtained of the product between the N2 and REM probability in a recording.</td>
</tr>
<tr>
<td>7</td>
<td>0.68</td>
<td>The time taken before 30% of the sum of the product between W and N2, calculated at every epoch, has accumulated, weighed by the total amount of this sum.</td>
</tr>
<tr>
<td>8</td>
<td>0.64</td>
<td>The time taken before 10% of the sum of the product between W and N1, calculated at every epoch, has accumulated, weighed by the total amount of this sum.</td>
</tr>
</tbody>
</table>
Validation to diagnose narcolepsy

Equivalent or better than MSLT in ~400 cases vs 2000 controls
Sleep and sleep disorder hardware

OLD

NOW

FUTURE

Customized flexible electrodes and circuitry
Flexible adhesive strip; wireless transmission

Zhenan Bao
Milder cases of narcolepsy type 1 without cataplexy are likely abundant in the general population but are rarely seen in sleep clinics.

- In sleep clinics only 15% of cases without cataplexy have low CSF hypocretin-1 (type 1 narcolepsy) but…
- Family studies have shown that although only 1% of first degree relatives, 2-4% of first degree relative have unexplained narcolepsy-like sleepiness without cataplexy.
- In the Wisconsin Sleep Cohort, a sample of about 1,000 subjects that has been studied over 20 years, 3 HLA positive subjects have narcolepsy-like feature, one with cataplexy (1/1000) and 2 without (2/1000).
### Narcolepsy spectrum of 237 trio families (ICSD3)

<table>
<thead>
<tr>
<th>EDS</th>
<th>Cataplexy</th>
<th>SL</th>
<th>SOREMPs</th>
<th>% HLA-DQB1*0602</th>
<th>Number of affected parents</th>
<th>% of affected parents</th>
<th>CSF Hcrt-1 in HLA+</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>&lt;8</td>
<td>≥2 (2), 1(1)</td>
<td>3/3 (100%)</td>
<td>3</td>
<td>0.7%</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>&lt;8</td>
<td>≥2</td>
<td>9/11 (82%)#</td>
<td>11</td>
<td>2.5%</td>
<td>*1L,1M</td>
</tr>
<tr>
<td>+/-*</td>
<td>-</td>
<td>≥8</td>
<td>≥2</td>
<td>1/5 (20%)</td>
<td>5</td>
<td>0.9%</td>
<td></td>
</tr>
<tr>
<td>4 (HLA+)</td>
<td>-</td>
<td>&lt;8</td>
<td>=1</td>
<td>12/17 (70%)</td>
<td>18</td>
<td>4.3%</td>
<td>*1L</td>
</tr>
<tr>
<td>1</td>
<td>-</td>
<td>≥8</td>
<td>=1</td>
<td>13/21 (62%)</td>
<td>23</td>
<td>4.5%</td>
<td></td>
</tr>
<tr>
<td>8 (2HLA+)</td>
<td>-</td>
<td>&lt;8</td>
<td>0</td>
<td>51/82 (62%)</td>
<td>87</td>
<td>17.7%</td>
<td>1N</td>
</tr>
<tr>
<td>17 (13HLA+)</td>
<td>-</td>
<td>≥8</td>
<td>0</td>
<td>153/276 (55%)</td>
<td>291</td>
<td>69.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>242/415 (58%)</td>
<td>438</td>
<td>438</td>
<td></td>
</tr>
</tbody>
</table>

*Suggest 0.8-2.3% of relatives without cataplexy are hcrt deficient (based on 3 documented low CSF hcrt-1 or on 11 excess of HLA positive)*

Yan Han and Fang Han, unpublished
Development of Cataplexy in cases without cataplexy within 2 years of onset

About 50% of cases with hypocretin deficiency at baseline will develop cataplexy within 30 years of onset versus 1% of non-hypocretin deficient cases.
Current Hypersomnia classification

• **Type 1 Narcolepsy:**
  – Hypocretin deficiency or cataplexy, MSLT SL ≤ 8 min, ≥ 2 SOREMPs

• **Type 2 Narcolepsy without cataplexy:**
  – Sleepiness, REM-related symptoms, MSLT SL ≤ 8 min, ≥ 2 SOREMPs; no other likely cause for sleepiness
  – Therapies better reimbursed by insurance companies

• **Idiopathic Hypersomnia (with or without prolonged sleep time):**
  – Sleepiness, no REM abnormalities or SOREMPs; no other likely cause for sleepiness
  – Typically increased sleep time (over 10 hours daily); if not, MSLT SL ≤ 8 min, 0-1 SOREMP

• **Periodic Hypersomnia**
Narcolepsy type 2 in clinics is indistinguishable from idiopathic hypersomnia

<table>
<thead>
<tr>
<th>Goldbart et al., 2015</th>
<th>Kappa (n=1135 MSLTs in 820 subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MSLT in control subjects</strong></td>
<td></td>
</tr>
<tr>
<td>≥ 2 SOREMPs</td>
<td>0.1 (0.0-0.3) ns</td>
</tr>
<tr>
<td>≥ 2 SOREMPs and MSLT ≤ 8 minutes</td>
<td>0.1 (-0.1-0.3) ns</td>
</tr>
<tr>
<td>Nocturnal SOREMP or (≥2 SOREMPs and MSLT ≤ 8 minutes)</td>
<td>0.2 (0.0-0.4) ns</td>
</tr>
</tbody>
</table>

Repeatability of the MSLT in Patients with Known CSF hypocretin Levels

- N=12 *hcrt deficient*, HLA positive, one without cataplexy, δ MSLT 1.19 ± 0.73, δ SOREMP -0.33 ± 0.26, 9/12 (75%) positive in both MSLTs, kappa=0.75
- N=11 normal CSF *hcrt*, 4/11 (36%) HLA positive, , δ MSLT -1.82 ± 0.97 , δ SOREMP-1.0 ± 0.45 , 3/11 (25%) positive in both MSLTs, kappa=0.00

OR 2 positive MSLTs *hcrt def/non def = 13.5 (95% CI: 1.8-101.1), p<0.01.

Ruoff et al., sleep medicine 2017
Large samples GWA on subjective sleep

• **Overlapping circadian genes found through GWA and basic biology**

• **Tight relationships with neuropsychiatry:**
  – Genetic architecture of Long sleep duration overlaps with that of Schizophrenia/bipolar
    • This complements our finding on KLS and TRANK1

• **May redefine some pathologies:**
  – Insomnia shares genetic architecture with anxiety
  – Restless leg syndrome shares MEIS1 and genetic architecture with insomnia

>>> Mandates studies with objective sleep
Need more research on therapies
Pathways to novel therapies

- Coming soon
  - Dual NE/DA reuptake inhibitors
  - H3 antagonists
  - Pentetrazole, a GABAergic agonist

- Hypocretin replacement therapies
  - Intravenous administration
  - Intranasal administration
  - Central administration
  - CNS transplantation

- Hypocretin agonists
  - Hcrt1 and Hcrt2 agonists

- Immune-based therapies
  - Steroid therapies
  - Intravenous-Immunoglobulins, plasmapheresis
  - Novel immunosuppressants such as Natalizumab
JZP-110 evaluation in Narcolepsy

\[(R)-2\text{-} \text{amino-3-phenylpropylcarbamate hydrochloride}\]

- Phenylalanine derivative
- DAT, NET reuptake inhibition
- Previously known as: YKP10A; R228060; 31,827; ADX-N05
Endogenous GABA modulator in CSF

• Clarithromycin
• Flumazenil

Rye et al., 2012; Trotti et al., 2015
Pentetrazole (GABA-A antagonist) evaluation in Narcolepsy

- GABA-A antagonist
- Proconvulsivant at high dose, but used at very low dose in the current trial
- Built on work by Lotti and David Rye suggesting existence of substance (unknown) potentiating GABAergic transmission in the CSF of patients with hypersomnia
- Also known as: BTD-001
- Recruiting patients now
CSF Histamine in Hypocretin-deficient vs -nondeficient Narcoleptic and Control subjects

P<.0001

Nishino et al., 2002
Pitolisant: H3 Inverse Agonist

2. Clinical Development Program in Narcolepsy
2.5 HARMONY III results

HARMONY III Efficacy Data on EDS and Others Symptoms

Mean length of exposure of 248 days (naive) and 678 days (non naive)

Frequency of all EDS symptoms were reduced vs. baseline over the 12m study

ESS score (n=99) improvement over the course of the study

Graph showing changes in EDS and other symptoms over 12 months.
Rescue of Narcolepsy-Cataplexy with hypocretin/orexin

Mieda et al., 2004
Hypocretin Agonist

OX2R: EC\textsubscript{50} = 28 nM
OX1R: EC\textsubscript{50} = 2750 nM
(Compound 30 in Ref 19)

Reduces cataplexy
Immunosuppression: Alternatives

• IVIG- doubtful efficacy: A problem is little is known regarding the natural evolution of the condition
• Steroids-no efficacy in two cases
• Alpha-4 integrin inhibitors: block T cell entry (but Progressive Multifocal Leukoencephalopathy)
• Anti CD3, anti CD20, anti-IL2R
• Anti-TCR idiotype antibodies would be ideal
• Preventing triggering events/surveillance
Modeling narcolepsy in a dish

Adding immune cells to reconstitute a personalized autoimmune model?
Sleep Analytics and Genetics in 30,000 samples

Supplementary sleep data
- Sleep schedule evaluation by actigraphy
- Sleep anatomy evaluation by photography

Subjective sleep data (ASQ)
- Sleep habits
- Sleep symptoms (e.g. sleepiness)
- Sleep Disorders (insomnia, OSA, Restless leg syndrome, narcolepsy, parasomnia)

Computerized Neurocognitive Battery (CNB)
- Attention, executive functions
- Performance Vigilance Tests

Objective Sleep Nocturnal Polysomnography (Sleep analytics, Machine learning)

Open source

Genetic data
GWAS, sequencing
Conclusion

• Narcolepsy type 1 is an autoimmune disease affecting hypocretin/orexin neurons
  – With cataplexy ~3/10,000; without cataplexy ~5/10,000 individuals, many undiagnosed
  – New diagnostic markers are coming (PSG, genetics, TCR sequencing, tetramers, isolation of T cells)
  – Genetic predisposition (HLA, TCR) implicates antigen presentation and autoimmunity via T cells
  – Upper airway infections such as H1N1 are triggering the process
  – Causal autoantigen is still elusive but closing in
  – Novel therapies, including agonists are in the pipeline

• Narcolepsy type 2 and idiopathic hypersomnia may be the same entity
  – Genetic overlap with psychiatric condition is suggested
  – Need more research, therapy is similar
Laboratory:
Lin Lin
Guo Luo

- NIH/NINDS rejected funding our lab for 2 years
- No more human narcolepsy research funded by NIH except a meaningless pilot project
- Last chance June 2018; after program terminated

Clinical and consortium collaborators in US, Taiwan, Korea, China, Europe, Japan
mignot@stanford.edu

Funding:
None
Jazz (PSG)