Targeted Therapies in Epilepsy

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Disclosures

- Trials supported by
  - Biocodex
  - Novartis
  - Sage Therapeutics

- I will discuss available data on targeted treatments in specific conditions which are off label or not standard therapy.
Objectives

- To discuss precision medicine in epilepsy in 2017
- To review targeted therapy in neurometabolic disorders, channelopathies, TSC and several specific gene disorders
- To review current state of pharmacogenomics in epilepsy
- Speculate about how treatment of epileptology will evolve over next few years
Epilepsy Challenges in 2017

- Seizures remain treatment resistant in 30-40% of individuals despite new AEDs and other advances.
- Surgery is underutilized.
- Cognitive and neuropsychiatric co-morbidity high.
- Mortality remains high.
- Epilepsy genetics shifting from academic pursuit of gene discovery to a clinical discipline based on molecular diagnosis and stratified medicine.
- However, in 2017 only a small percentage of patients benefit from precision or targeted therapies.
Goals of Epilepsy Treatment

- Cure of disease
- Control of seizures with absence of side effects
- Balance of therapeutic effect and side effects, costs and benefits
Treatment of Epilepsy in 2017

- Anti-seizure medications
- Dietary therapies
- Surgery
- Brain Modulation
  - Vagus nerve stimulation, Deep brain stimulation, Responsive stimulation
- Thermocoagulation
- Precision treatment guided by genomics
- Repurposing of other drugs
Epilepsy in Children: Impact on Learning

- Prospective cohort of children with epilepsy diagnosed < 8 years
- Early age at seizure onset and pharmaco-resistance resulted in lower IQ
- Pharmaco-resistance had most profound impact in 0-3 year group

Berg et al., Neurology 2012
Precision Medicine: Francis Collins

- Medicine for most of human history has been one-size-fits-all. But we’re all different, and we’re finding out that the diseases we have lumped together under one label are actually at the molecular level quite distinct.

- Precision medicine tries to understand what’s underneath those disease layers and tries not to lump everyone together but think about individual differences.
Essence of Precision Treatment

- Is it possible to predict which patients will respond best to a specific treatment?
- Is there a specific or novel therapy for individual based on genes or pathway involved in causing their epilepsy?
- Can we predict which patients will develop side effects of treatment?

EpiPM Consortium Lancet Neurol 2015; Symonds et al. Current Opin Neurol 2017;
Treataable Neurometabolic Diseases

- Rare diseases
- Important not to miss diagnosis
- Number of treatable metabolic diseases increasing (now ~84)
- Newborn screening detects some disorders
- Major research interest of team at BCCH (Treatable Intellectual Disability Endeavour - TIDE)
- App available to guide physicians with investigations
Inherited Metabolic Epilepsies

- Vitamin responsive (B6, PNP, Biotinidase)
- Transporter (GLUT1, Cerebral Folate)
- Aminoacid and organic disorders (Serine synthesis, Creatine synthesis)
- Mitochondrial disorders (KD)
- Urea Cycle disorders
- Neurotransmitter disorders
- Disorders of glucose homeostasis
Pyridoxine Dependent Epilepsy

- Historically diagnosis trial of pyridoxine
- Biomarkers: urine AASA
- Testing for Antiquitin gene mutations
- Can be diagnosed with NGS

- Treatment with pyridoxine alone not effective in all patients
GLUCOSE TRANSPORTER 1 Deficiency: Variable Clinical Features (SLC2A1)

**Neonate**
- Main manifestations:
  - Seizures
  - Apnea
  - Abnormal eye movements

**Older children**
- Paroxysmal:
  - Alternating hemiplegia
  - Intermittent ataxia
  - Headache, confusion
- Permanent:
  - Mental retardation
  - Ataxia
  - Spasticity
Creatine Def Syndromes (CDS)
GAMT, AGAT, CRTR
Sodium Channel Disorders (SCN)

- In CNS: 4 major SCN family
  - SCN1A (Nav1.1, 2q24): Dravet syndrome (DS), FS+, FHM3, SUDEP
  - SCN2A (Nav1.2, 2q24): BFNIS, GEFS+, MFEI, OS, EOEE, DS
  - SCN3A (Nav1.3, 2q24): Unclear
  - SCN8A (Nav1.6, 12q13): EE

Brunkaus A et al., J Med Genet 2014
Dravet Syndrome

- 1978: 1st described by Charlotte Dravet
- Seizure onset: 1st year of life
- Hemiclonic or generalized TC seizures
- Other seizure types
- Normal development prior to seizure onset
- Moderate to severe intellectual impairment
  Ataxia and crouched gait
- Mortality ~ 10%
<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Gene</th>
<th>Impact on Management</th>
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</thead>
<tbody>
<tr>
<td>Dravet Syndrome</td>
<td><em>SCN1A</em></td>
<td>Antiepileptic medication change</td>
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<tr>
<td>Alpers Syndrome</td>
<td><em>POLG</em></td>
<td>Stopped valproic acid, early palliative care</td>
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<tr>
<td>Self limited familial neonatal epilepsy</td>
<td><em>KCNQ2</em></td>
<td>Stopped antiepileptic medication</td>
</tr>
<tr>
<td>Adenylsuccinate Lyase Deficiency</td>
<td><em>ADSL</em></td>
<td>Earlier consideration to use ketogenic diet; S-Adenosyl-L-methionine trial</td>
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<tr>
<td>Hemiplegic Migraine Epilepsy</td>
<td><em>ATP1A2</em></td>
<td>Stopped stiripentol; started flunarazine</td>
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<tr>
<td>KCNQ2 Encephalopathy</td>
<td><em>KCNQ2</em></td>
<td>Antiepileptic medication change</td>
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<tr>
<td>CDG IIIm</td>
<td><em>SLC35A2</em></td>
<td>Galactose trial</td>
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Treatment of Dravet Syndrome

- Seizures treatment resistant in most patients
- Best options: Clobazam, Valproic acid, Topiramate, Stiripentol, Levetiracetam
- Ketogenic diet
- Avoid: Carbamazepine, Oxcarbazepine, Phenytoin, Lamotrigine, Vigabatrin, Phenobarbital, Rufinamide
Stiripentol

- Modulator of GABA

- Potentiates GABAergic inhibitory post-synaptic currents, maintaining phasic inhibition (by action on α4 GABA_A receptors and tonic inhibition)
## Stiripentol

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Dressler et al. 2015</td>
<td>Open label, retrospective</td>
<td>9</td>
<td>All treated with VPA + CLB + STP Responder rate 89%, mean sz reduction 73%</td>
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<tr>
<td>Inoue et al. 2014</td>
<td>Open-label, prospective</td>
<td>24</td>
<td>67% responders (17% sz-free) Significant reduction in sz duration and use of rescue meds</td>
</tr>
<tr>
<td>Wirrell et al. 2013</td>
<td>Open-label, retrospective</td>
<td>82</td>
<td>Overall sz frequency reduced in 57-80% depending on co-therapy All had reduction in frequency of prolonged szs and most had significant reduction in rescue med use and ER visits/hospitalizations</td>
</tr>
<tr>
<td>Inoue et al. 2009</td>
<td>Open label, prospective</td>
<td>23</td>
<td>&gt;50% reduction in GTCS in 61% (9% sz free)</td>
</tr>
<tr>
<td>Thanh et al. 2002</td>
<td>Open-label, retrospective</td>
<td>46</td>
<td>Seizure frequency decreased by 66% (p&lt;0.001) Reduction in sz duration (p&lt;0.002), status epilepticus (p&lt;0.001)</td>
</tr>
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</table>
Fenfluramine

- Amphetamine-like agent used as anti-obesity drug
- Taken off market due to possible cardiac adverse effects (valve thickening, pulmonary hypertension)
- Releases serotonin by disrupting vesicular storage and reversing 5HT transporter function
Fenfluramine

- 12 pts treated (mean dose 0.34, range 0.12-0.90 mg/kg/d) for mean of 11.4 yrs (range 1-19 yrs)
  - No pt had received STP, ketogenic diet or bromide
  - 10 (83%) continued on fenfluramine at follow-up
  - 7 (58%) were seizure free for longer than 1 year

- Side effects:
  - Mild, non-progressive heart valve thickening in 2
  - Decreased appetite in 2

Ceulemans et al. Epilepsia 2012
Fenfluramine Studies in DS

- Prospective studies
- Children on VPA and Clobazam
  - 75% reduction in major seizures
- Children on Stiripentol, Clobazam, VPA
- Study in Lennox-Gastaut syndrome
- Probable study in adults with DS
KCNQ2 Related Epilepsy

- Phenotypes:
  - Benign familial neonatal epilepsy
  - Epileptic encephalopathy

- Encodes potassium voltage-gated channel subfamily KQT member 2

- Drugs which act on sodium channels such as carbamazepine and phenytoin often effective

- Retigabine shown to be effective in some patients
Adverse Effects of Retigabine

- Blue skin discoloration and retinal pigment abnormalities
- Urinary retention
KCNT1 Mutations

- **KCNT1**: encodes a weak voltage-dependent and intracellular sodium-activated potassium channel.
- **Missense mutations**:  
  - Autosomal dominant nocturnal frontal lobe epilepsy
- **De novo gain of function**:  
  - Migrating focal epilepsy of infancy
Quinidine in KCNT1 Mutations

- Made from Cinchona plant
- Broad spectrum K channel blocker (KCNT1)
- Anti arrhythmic
- Patients with malignant migrating epilepsy have responded to 34-60mg/kg/day
- Case reports of patients having improvement in seizures and development with gain of function mutations
Targeted Therapy in Tuberous Sclerosis Complex

cortical tubers

cytomegalic neurons

and balloon cells

mTOR pathway
Tuberous Sclerosis Complex (TSC)

- 90% develop epilepsy
- Onset often in 1st year of life
- Uncontrolled epilepsy: high risk of autism and intellectual impairment
- Advances: Biomarkers of epilepsy and treatment prior to seizure onset
- mTOR inhibitors effective for epilepsy
Problems in TSC

- How do we predict which patients will do well with surgery?
- When to use KD which has mTOR inhibition?
- What is role of mTOR drugs in epilepsy and how to access them?
mTOR Inhibitors and Epilepsy

- **TSC mouse models:**
  - Rapamycin reversed astrogliosis/neuronal disorganization
  - Prevent development of seizures
  - Improve learning and attention

- **Clinical trials:**
  - Rapamycin reduced seizure frequency
  - Everolimus Phase 1/2 and EXIST-1 SEGA trials showed reduction of seizures in some patients
  - EXIST 3 trial: Everolimus effective in reducing seizures
Tubers

- Tubers are dynamic entities that evolve over time?
  - Cyst-like cortical tubers progress on MRI
  - Display reactive gliosis on pathology consistent with a chronic process
- Elevated mTOR activity in tubers
Exist 3 Trial in TSC

366 patients:
placebo (n=119), low dose (n=117) or high dose (n=130)

>50% sz frequency reduction
15.1% placebo
28.2% low dose
40% high dose

Median percentage reduction in sz frequency:
14.9% with placebo
29.3% low exposure
39.6% high exposure

mTOR Pathway and Other Disorders

- Tuberous sclerosis Complex
- FCD
- Focal epilepsy without normal imaging
- Post-traumatic epilepsy
- Polyhydramnios megalencephaly symptomatic epilepsy syndrome
- Neurofibromatoses 1 and 2, Peutz-Jeghers syndrome
- Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome
- Proteus syndrome Lhermitte-Duclos syndrome, von Hippel-Lindau syndrome
- Huntington’s, Parkinson’s, Schizophrenia,
- Alzheimer’s
- Learning and memory
Role of mTOR Inhibitors

Reports of seizure control:
- Focal Cortical Dysplasia (esp FCD II)
- Polyhydramnios, Megencephaly and Symptomatic Epilepsy
- Hypothalamic Hamartoma
Focal Cortical Dysplasia: Genetic Aspects

- Somatic and germline mutations
- Familial or sporadic
  - GATOR 1 (11%)
  - 1q21.1-q44 duplication affecting AKT3
- DEPDC5: 8% of focal epilepsy
  - +/- focal cortical dysplasia I, IIA, IIB
  - Seizures from variable foci
- NPRL2 and NPRL3: 1–3% of focal epilepsy;
DEPDC5 and GATOR1 Mutations in Focal Epilepsy

- **Focal epilepsies**
  - DEPDC5
  - NPRL2
  - NPRL3
  - Other

- **Familial focal epilepsies with FCD**
  - DEPDC5
  - NPRL2
  - NPRL3
  - Other
mTOR Inhibitors in Post-traumatic Epilepsy

- Changes in brain involve mTORC1 activation:
  - Axon sprouting, increased synthesis and phosphorylation of proteins, cell migration, and neurogenesis

- TBI mouse model studies with rapamycin:
  - GABAergic inhibition
  - Reduce mossy fiber sprouting and excitation of dentate granule cells
  - Decreased seizure frequency
Pharmacogenomics in Epilepsy

• How genetic factors affect response to treatment - efficacy and adverse drug reactions

• Genetic categories of variation:
  • Drug pharmacokinetics, drug pharmacodynamics, epilepsy genes, ? Other

• Impact of NGS on pharmacogenomics in epilepsy and precision medicine yet to come
  • Collaborative projects: EpiPGX, CPNDS (The Canadian Pharmacogenomics Network for Drug Safety)
# Influence of genetic factors on response and adverse reactions to AEDs: established evidence

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Genetic Factor</th>
<th>Effect</th>
<th>Recommendations</th>
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</thead>
<tbody>
<tr>
<td>Pharmacokinetics &amp; Pharmacodynamics</td>
<td>Variation in CYP2C9 (*2/*3)</td>
<td>Risk of developing concentration-dependent neurotoxicity from phenytoin</td>
<td>Pre-treatment genetic testing not routine&lt;br&gt;Monitor clinically and drug levels</td>
</tr>
<tr>
<td>Epilepsy Genes</td>
<td>Mutations in SLC2A1</td>
<td>GLUT-1 deficiency</td>
<td>CSF/genetic testing ketogenic diet</td>
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<tr>
<td></td>
<td>Bi-allelic mutations in ALDH7A1</td>
<td>B6-dependent epilepsy</td>
<td>AASA/genetic testing Pyridoxine or pyridoxal 5’ phosphate</td>
</tr>
<tr>
<td>Other</td>
<td>HLA-B*15:02</td>
<td>SJS and TEN induced carbamazepine/other aromatic AEDS in patients from Han Chinese, other South Asia groups</td>
<td>Pre-treatment testing groups at risk (Level A)&lt;sup&gt;a&lt;/sup&gt;&lt;br&gt;If positive-use alternative as 1&lt;sup&gt;st&lt;/sup&gt; line</td>
</tr>
<tr>
<td></td>
<td>HLA-B*13:01</td>
<td>Increased risk carbazmepine-induced hypersensitivity reactions-European, Japanese, all ancestries</td>
<td>As above except all ancestries (Level B)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>S Balestrini & S Sisodiya Neuroscience Letters 2017.  <sup>a</sup>Amstutz U et al Epilepsia 2014.
Subject 033

- 9 month presentation focal status-left arm
- Development normal
- Family history febrile seizures in father, paternal aunt and paternal great uncle
- Failed 5 anti-seizure medications
- MRI, neurometabolic, microarray negative
033 - Genetic Findings 4 weeks

- Compound heterozygous mutations in POLG (each inherited by a parent)
  - likely pathogenic
  - ALPERS syndrome

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Position</th>
<th>rs ID</th>
<th>Reference</th>
<th>Exon</th>
<th>Mutation</th>
<th>Allele</th>
<th>Position</th>
<th>Phenotype</th>
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<tbody>
<tr>
<td>POLG</td>
<td>chr15:89866657</td>
<td>C/G</td>
<td>rs113994097</td>
<td>C/TDDD</td>
<td>NM_001126131</td>
<td>exon13</td>
<td>c.G2243C</td>
<td>p.W748S</td>
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<tr>
<td>POLG</td>
<td>chr15:89871929</td>
<td>C/G</td>
<td>novel</td>
<td>C/DDDD</td>
<td>NM_001126131</td>
<td>exon5</td>
<td>c.G1157C</td>
<td>p.R386P</td>
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</table>
The proband is a compound heterozygous for two *POLG* mutations—likely pathogenic—ALPERS syndrome!

**POLG**
- **chr15:89866657**
  - **C/G**
  - **rs113994097**
  - **C/T**
  - **DDD**
  - **NM_001126131**
  - **exon13**
  - **c.G2243C**
  - **p.W748S**

**POLG**
- **chr15:89871929**
  - **C/G**
  - **novel**
  - **C/DDDD**
  - **NM_001126131**
  - **exon5**
  - **c.G1157C**
  - **p.R386P**

Immediate clinical impact (valproic acid)
rxSEEK™ Epilepsy

<table>
<thead>
<tr>
<th>Category</th>
<th>Standard Precautions</th>
<th>Use With Caution</th>
<th>Consider Alternatives</th>
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<tbody>
<tr>
<td>Anticonvulsants</td>
<td>Cannabidiol (Epidiolex)</td>
<td>Fosphenytoin (Cerebyx)</td>
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<tr>
<td></td>
<td>Carbamazepine (Tegretol, Carbrol, Epitol)</td>
<td>Phenytin (Dilantin)</td>
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<td>Elicitzabpine (Aptiom)</td>
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<td>Ethosuximide (Zarontin)</td>
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<td>Ezogabine (Potiga)</td>
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<td>Felbamate (Felbatol)</td>
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<td>Gabapentin (Neurontin)</td>
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<td>Lacosamide (Vimpat)</td>
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<td>Lamotrigine (Lamictal)</td>
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<td>Levetiracetam (Keppra)</td>
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<td></td>
<td>Oxcarbazepine (Trileptal, Oxtellar XR)</td>
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<td>Perampanel (Fycompa)</td>
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<td>Phenobarbital (Luminal)</td>
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<td>Pregabalin (Lyrica)</td>
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<td>Primidone (Mysoline)</td>
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<td>Rufinamide (Banzel)</td>
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<td>Stripentol (Diacont)</td>
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<td>Tiagabine (Gabitril)</td>
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<td></td>
<td>Topiramate (Topamax)</td>
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<td></td>
<td>Valproic Acid (Depakote, Depakene)</td>
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<td>Vigabatrin (Sabril)</td>
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<td>Zonisamide (Zonegran)</td>
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<td>Benzodiazepines</td>
<td>Clobazam (Onfi)</td>
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<td></td>
<td>Clonazepam (Klonopin)</td>
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<td>Diazepam (Valium)</td>
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Potential Treatments

- Clemizole: Dravet
  - histamine antagonist
- Bryostatin: KCNT1
  - Macrolide lactone: inhibit K current
- Silencing microRNAs: sz & neuroprotective results
  - regulate post-transcriptional expression of protein coding mRNA, dendritic spine morphology
- SAGE 217: Dravet, Rett syndrome
The Future

• Early diagnostic NGS in early onset epilepsy or epilepsy of unknown cause
• Drugs targeted towards genetic defect or molecular pathway or to bypass the pathway disturbed by genetic variant
• Functional test systems measuring single gene targets and multicomponent networks will be required
• Pharmacogenomics essential to reduce side effects in both patients and embryos at risk
• Potential for further novel or repurposed therapies akin to "Personalized Oncogenomic Program"
• Malformations of brain development and prevention of post traumatic epilepsy: Use mTOR inhibitors in the future

Rosenow et al. Epil Behav 2017; Bauer et al. Epil Behav 2017; Lindhout Lancet Neurol 2015;