LEARNING OBJECTIVES

After this education, learners should be able to:

- Describe the rationale for targeting the KNDy neuron complex for new therapeutic interventions for menopausal symptoms
- Understand potential side effects from KNDy neuron therapeutics
- Describe what is known about drugs in the pipeline that target KNDy

KNDY NEURONS SECRETE NEUROPEPTIDES

- Kisspeptin: G-protein coupled receptor ligand neuropeptide (gene kiss1)
- Neurokinin B: endogenous peptide ligand that belongs to the family of tachykinin peptides (gene TAC) highest affinity NK3R
- Dynorphin: kappa opioid
- KNDy neurons are co-localized with > 95% of ER, PR, AR in arcuate nucleus

DISCLOSURES

Disclosures:
- Royalties from online UpToDate, Scientific American, and ACP Smart Medicine
- Research funding from NIH, Bayer
- No COI

Trade Names:
Every attempt made to present in a nonbiased fashion

Definitions:
- K = Kisspeptin
- N = Neurokinin B
- Dy = Dynorphin
- PRKA = peripherally restricted kappa agonist
- NK3R = neurokinin 3 receptor
- NK1R = neurokinin 1 receptor
WORKING HYPOTHESIS

Hyper-activation of KNDy neurons induces Hot Flashes

KNDy neurons are interconnected

KNDy neurons are interconnected

NKB activates

DYN inactivates
**SILENCING KNDy NEURONS**

- **Blocking the NK3R with NK3R-antagonist reduces KNDy Activity**

- **Stimulating the KOR receptor with KOR agonist increases the impact of the Dynorphin KNDy inactivation pathway**

**CLINICAL APPLICATIONS OF KNDy NEURON MANIPULATIONS**

- **NKB agonists result in HF pre-MP** (Jayasena, 2015)
- **NKB antagonists suppress HF PMP** (Prague, 2017)
- **Genetic variations in the gene that encodes NKB are associated with variations in VMS frequency** (Crandall, 2017)
- **Kappa antagonists ↑ LH pulsatility rats** (Nakahara, 2013; Mosari, 2013)
- **Kappa agonists ↓ LH pulsatility and ↓ HF** (Oakley, 2015)

**KNDy HOT FLASH RX PIPELINE**

- **NK3R antagonists**
  - **MLE 4901**
  - **ESN364**
- **Dual NK1R/NK3R antagonist**
  - **NT-814**
- **PRKA** (peripherally restricted kappa agonists)

**HISTORY NK3R ANTAGONIST DRUGS**

- **Ganetant-SR-142801**: NK3R antagonist, nonpeptide developed for schizophrenia and drug addiction (blocked effects of cocaine in anima models) Emonds-Alt X. SR 142801, the first potent non-peptide antagonist of the tachykinin NK3 receptor. Life Sciences1995,56 (1): PL27–32.
- **Pavinetant-MLE-4901**: NK3R antagonist neuropeptide developed initially for schizophrenia, then HF, PCOS
- **Talnetant SB-223,412**: developed for schizophrenia and irritable bowel syndrome
**NK3R ANTAGONIST STRUCTURES**
- Osanetant SR-142, 801
- Pavinetant MLE 4901
- Fezolinetant ESN364 (HF)
- NT-814 (HF)

**MLE 4901, PAVINETANT**
Oral twice daily selective NK3R antagonist developed for schizophrenia, hot flashes (NCT02668185), PCO

- November 2017
- Discontinued - Phase-II for Hot flashes in United Kingdom and Phase-II for Polycystic ovary syndrome in USA, Germany, United Kingdom
- Phase II trial for Hot flashes in United Kingdom showed the clinical risks exceeded benefits
- Abnormal liver function
- Plan to reformulate and reintroduce ~ 3 yr

http://adisinsight.springer.com/drugs/800038259

**Phase 2a study postmenopausal women**

**Frequency, severity, bother, interference**

Prague J, Lancet 2017

Prague J, Menopause 2018
**ESN364, FEZOLINETANT**

- Selective NK3R antagonist
- Oral twice daily
- Phase 1, 2a trials for menopause
- Phase 2a trials PCOS
- Phase 2 trials uterine fibroids

Fraser G. J Clin Endocrinol Metab 2016
Fraser G. Endocrinol 2015
https://bciq.biocentury.com/products/fezolinetant

---

**ESN364, FEZOLINETANT**

**Phase 1 studies healthy men and women**

- RCT 6:2 blinded, N=64 men single ascending dose
  - 3, 6, 12, 23, 46, 90, 180 mg
- RCT 6:2, N=24 men, 10 days
  - repeat dose 20, 60, 180
- RCT 6:2, N=24 women, 21 days
  - repeat dose 20, 60, 180

**Findings**
- Rapid absorption (t<sub>max</sub> 3-4 hours repeat dosing)
- Linear PK (no accumulation on repeat dosing)
- Short half life (4.4-6.3 hr in women, repeat dosing)
- Dose response effect on reproductive hormones (LH, E2, P, T)
- ↓endometrial thickening, delayed/impeded ovulation, prolonged cycle duration

---

**ESN364, FEZOLINETANT**

**Phase 2 studies postmenopausal women**

- Phase 2a, 12 week RCT, N=80
  - moderate-severe HF
  - 90 mg bid
- **Findings**
  - LH ↓50% (vs 16%), p <0.001
  - VMS frequency ↓93% (vs 54%), p <0.001
  - VMS severity ↓94% (vs 46%), p <0.001
  - Safety no SAEs, AEs similar between groups
- Phase 2b, 12- week RCT 1:6, N=352, NCT03192176 , 51 sites
  - 8 cohorts: Plcbo vs qd (4 doses) vs bid (4 doses)
  - dose range 30 - 180 mg/d
  - ONGOING, anticipate completion August 2019

Fraser G. ENDOABSTRACT 2017
Clinicaltrials.gov

---

**ESN364, FEZOLINETANT**

**Sleep**

- Phase 2a 12 week RCT, N=80
  - 90 mg bid
- **Findings**
  - sleep improved ESN364 (vs placebo) p<0.001

**Weight loss**

- Cynomolgus monkeys, N=12, 12 weeks
  - RCT
  - dose range 50-100 mg/kg/d vs vehicle control
- **Findings**
  - ESN364 1% ↑total body weight (vs 12% ↑control)

Fraser G. ENDOABSTRACTS 2017
EFFICACY ON HOT FLASH FREQUENCY
ESN364, FEZOLINETANT

EFFICACY ON HOT FLASH SEVERITY
ESN364, FEZOLINETANT

NT-814
NK1R, NK3R ANTAGONIST

- Selective NK1R, NK3R antagonist
- Oral once daily
- Patent for “sex hormone dependent diseases”
- Phase 1, 2a trials for menopause
- Phase 2a trials PCOS

NT-814
NK1R, NK3R ANTAGONIST

Phase 1 study healthy men
- Single blind, RCT, N=14
- Doses: 10, 30, 60, 120, 160, 160-250 mg
- Findings
  - long t1/2 ~ 15 hr
  - rapid absorption at doses < 60 mg, ~ 1 hr
  - doses > 120 mg, t max ~ 4-5 hours
  - NK1R occupancy, EC50 0.875 ng/mL
  - NK3R occupancy, EC50 8.75 ng/mL
- Safety: Increase somnolence, headache

https://clinicaltrials.gov/ct2/show/NCT02865538

https://www.gsk-clinicalstudyregister.com
**NT-814 NK1R, NK3R ANTAGONIST**

**Phase 1 study healthy men and women**
- Open label, 3-way cross over, N=16
- Dose 100 mg, 200 mg, placebo (with food)
- **Findings**
  - long t 1/2 ~ 26 hr
  - rapid absorption, t max ~ 1 hr, both doses
- Safety (42 doses across groups)
  - 9/42 somnolence (21%) vs 0/12 placebo
  - 9/42 headache (21%) vs 5/12 placebo
  - 2/42 dizziness (5%) vs 0/12 placebo

**NT-814**

**Phase 2a study postmenopausal women**
- Double blind RCT 14 days, N=80
- Doses: 20 subjects each, placebo vs 50, 100, 150 and 200 mg
- Primary outcome: pharmacokinetics
- Secondary outcome: VMS, LH serum concentration

---

**NT-814, DAYTIME HOT FLASH FREQUENCY**

- Number of moderate and severe day time hot flashes recorded in a diary in the evening
- Median Reduction in HF Frequency in Week 2 – All Doses

**PERIPHERALLY RESTRICTED KAPPA AGONISTS**

- The pulsatile activity of KNDy neurons is controlled by an interplay of NKB receptors and dynorphin receptors, acting in a reciprocal fashion to generate pulsatile events—intermittently stimulated by NKB and suppressed by dynorphin
- Kappa agonists bind the dynorphin receptor (AKA kappa opioid receptor, KOR), and inhibit LH pulses, presumably by interfering with kisspeptin and GnRH signaling
- KOR receptor antagonists stimulate LH pulse frequency
- Pure kappa agonists cause dysphoria and nausea, **peripherally restricted kappa agonists (PRKAs)** do not
- KNDy neurons are located at the interface of the blood brain barrier and may be a target for PRKAs that do not pass the blood brain barrier
- **Hypothesis: PRKAs are effective in treating HF and have minimal side effects**
PERIPHERALLY RESTRICTED KAPPA AGONISTS

- Clinical observations suggest postmenopausal women on methadone and some opioids may have ↓ hot flashes and opioid withdrawal ↑ hot flashes (Reed clinical experience)
- Kappa agonists bind to the opioid receptor in the hypothalamus and inhibit KNDy neuronal activity (Navarro, 2009; Wakabayashi, 2010)
- Peripherally restricted kappa receptor agonists (PRKA)s do not cross the blood-brain barrier and could theoretically block hot flashes without affecting cognitive brain centers, avoiding opioid side effects (Chen, 2005, Chavkin, personal communication, 2012)

THE BRAINS

Double-blind, randomized cross-over study, inpatient research setting, N=12
Moderate-severe hot flashes, ages 48-60
3 interventions in randomized order, on 3 separate days:
- placebo
- standard Pentazocine/Naloxone (50/0.5 mg) or low-dose Pentazocine/Naloxone (25/0.25 mg)
- IV catheter for luteinizing hormone (LH) blood sampling
- Skin conductance and Holter monitors placed
- Subjective hot flash frequency and severity recorded

LH PULSE AND HOT FLASH OCCURRENCE

Oakley AE. Menopause, 2015
SUMMARY KNDY NEURON MANIPULATION

<table>
<thead>
<tr>
<th>Drug</th>
<th>HF freq</th>
<th>HF sever</th>
<th>QOL</th>
<th>Sleep</th>
<th>Sexual function</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLE 4901</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>LEEDS</td>
<td>No change</td>
<td>LFTs</td>
</tr>
<tr>
<td>(Prague J)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(sexual function domain, MENQOL)</td>
<td></td>
</tr>
<tr>
<td>ESN064</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>HRDIS</td>
<td>No change</td>
<td>No diff from plcbo overall, G1 14% vs 0% plcbo</td>
</tr>
<tr>
<td>(Fraser G)</td>
<td></td>
<td></td>
<td></td>
<td>Greene</td>
<td>(sexual function domain, Greene)</td>
<td></td>
</tr>
<tr>
<td>NT-814</td>
<td>↓</td>
<td>↓</td>
<td>?</td>
<td>LEEDS</td>
<td>No change</td>
<td>Mild somnolence higher dose</td>
</tr>
<tr>
<td>(Anderson R, Pawsey S)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(sexual function domain, Greene)</td>
<td></td>
</tr>
<tr>
<td>KAA</td>
<td>↓</td>
<td>-</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>Dysphoria, nausea</td>
</tr>
<tr>
<td>(Oakley A)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SUMMARY KNDY INTERVENTIONS

- Rapid effect within 3 days, full effect within 7-14 days
- Observed efficacy appears greater than any other proven non-hormonal product (SSRI, SNRI, or gabapentin)
- Single oral daily dose desired
- Side effect profiles promising, but are currently limiting further development of some products (e.g. Millendo, MLE 4901, Pavinetant)
- Long term studies will determine whether this class of drugs will become part of our RX armamentarium
REMAINING QUESTIONS

- If overall LH is decreased by KNDy RX, what effect will this have on postmenopausal androgens and sexual function?
- NK3 receptors are present throughout the brain and the body (e.g., liver). How to target just KNDy neurons and the adjacent thermoregulatory center with these novel therapeutics?
- Will drug development be handicapped by the ubiquitous nature of NK receptors or will this be a bonus in the end (e.g., improved metabolic profile, sleep)?
- PRKAs theoretically hold promise, but will they hold up to the test of time (rigorous RCTs)?