Clexio Biosciences

CLE-400 - a potent alpha-2 adrenergic receptor agonist for the treatment of chronic itch

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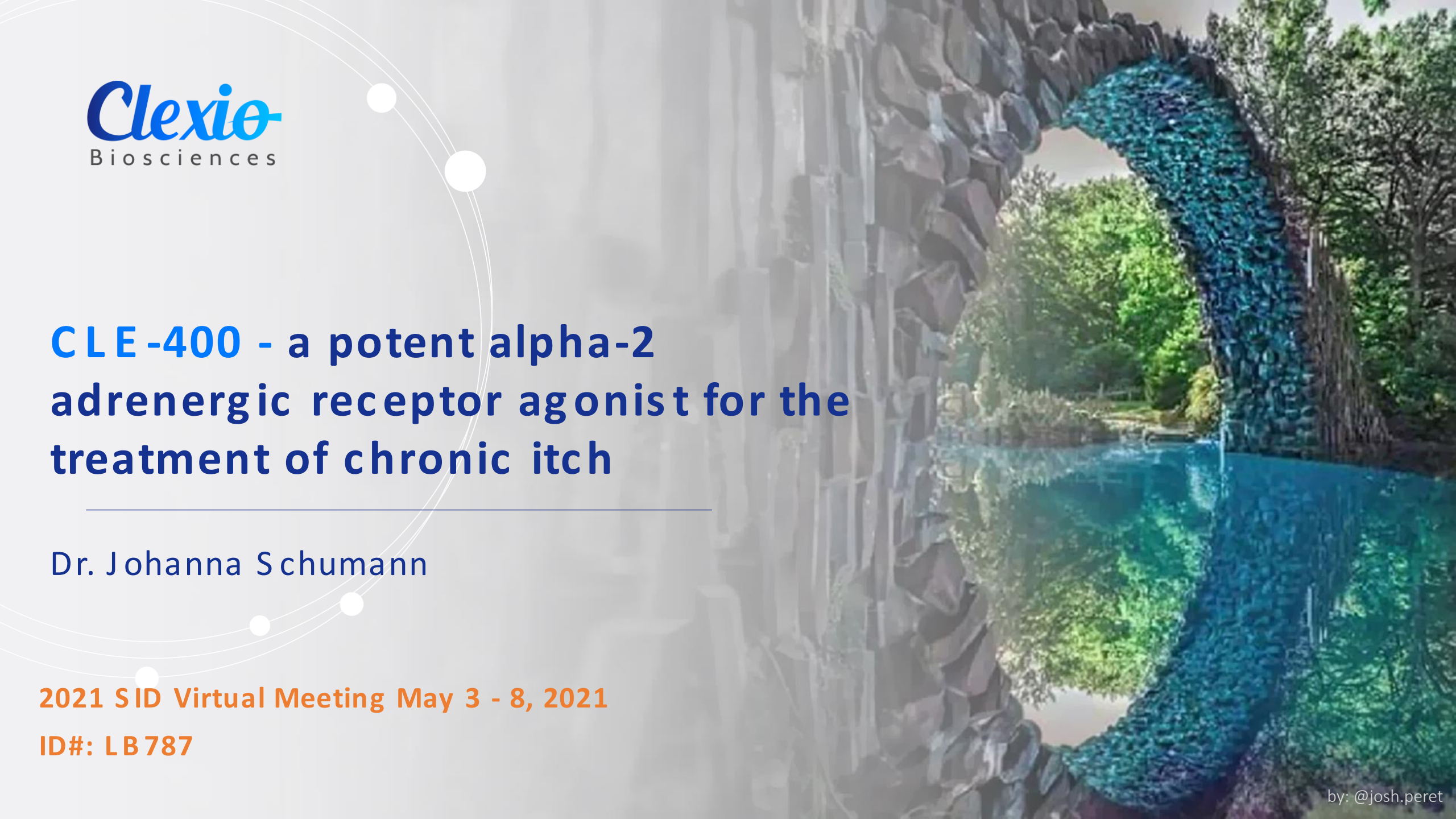

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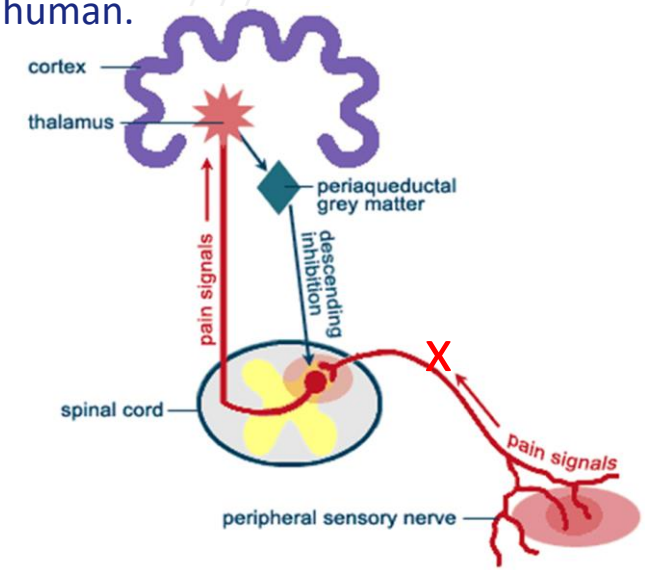
CLE-400: a Novel, Non-Opioid Topical Treatment for Chronic Pruritus

- **A New Molecule for Pruritus: CLE-400 is a new investigational drug that has not been approved for commercial distribution.** CLE-400 is an aqueous gel of detomidine, a potent α2-adrenergic agonist activating additional potentially therapeutically relevant targets (SST4, H4).
  - Detomidine is approved as a systemic medication for veterinary use. Never developed for human.
- **Targeting α2-adrenergic receptors peripherally**
  - Systemically administered α2-adrenergic agonists have shown anti-pruritic effect in preclinical model. But limited use to invasive RoA and systemic AEs
  - Clexio's Immunohistochemistry studies demonstrated that **α2-ARs, H4R and SST4R are expressed in pig skin**.
  - Activation of α2 receptors could produce anti-pruritic effects **by inhibiting the excitability and neural signaling from the peripheral nociceptors/pruriceptors (C-fibers) to the brain**



- The technology: CLE-400 gel formulation was developed to deliver **high dermal concentrations over an extended period of time (depot effect in the skin**) while maintaining limited systemic exposure

CLE-400: novel topical treatment for Chronic Pruritus

Pruritus (itch) is a common and distressing symptom of several dermatological and non-dermatological conditions. Pruritus may result in sleeplessness, inability to work, aggression, anxiety, depression and low quality of life

23-44 million Americans are estimated to suffer from chronic pruritus due to cutaneous or systemic conditions[1]

No FDA-approved treatment and limited research, especially on neuropathic itch

Pathophysiological sub-types:

- Dermatological, Systemic, Psychogenic
- Neuropathic (BRP, NP, Post-burn…)

CLE-400

Safe and efficacious treatment options are limited for the treatment of chronic itch.

CLE-400 has a potential to become first topical treatment given the lack of approved therapies and great unmet need

1. Mollanazar, Nicholas K., Savannah Dean Koch, and Gil Yosipovitch. "Epidemiology of chronic pruritus: where have we been and where are we going?." Current Dermatology Reports 4.1 (2015): 20-29

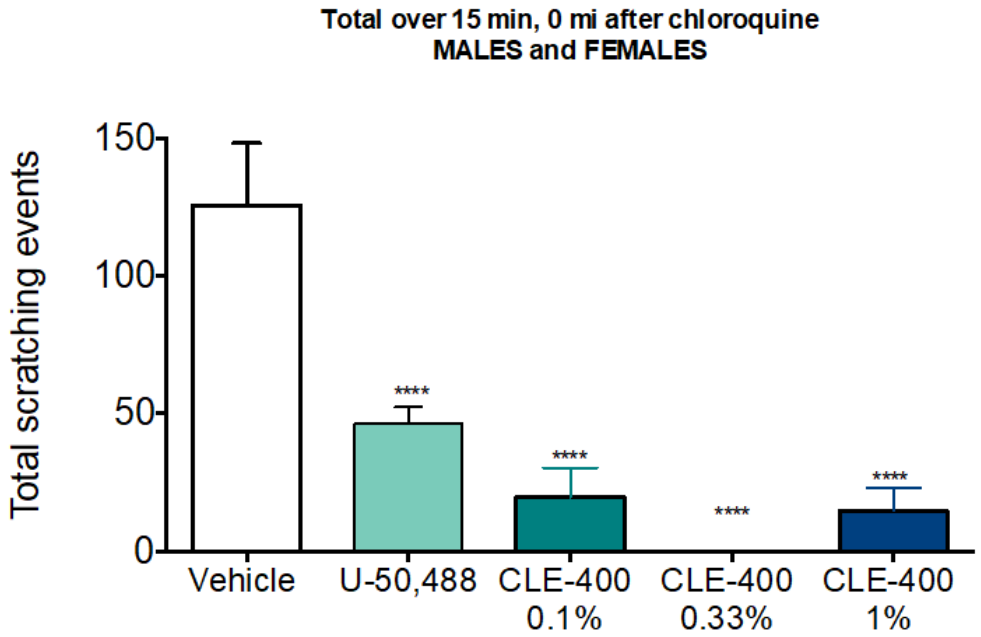
Detomidine: a Potent α2-Adrenergic Receptor Agonist

- Clexio conducted binding and functional assays with Detomidine against a wide range of molecular targets (G-protein coupled receptors, ion channels, transporters, enzymes) in order to better understand its MOA.
- Detomidine has been confirmed to potently activate α2A adrenergic receptors in vitro
- Clexio also discovered that detomidine activates 2 secondary targets , histamine 4 (H4) and somatostatin 4 (sst4) receptors.
- Detomidine's targets have been shown to be expressed in the skin

Receptor	Source	Activity	Detection method (Incubation)	Measured Component	Potency
$\alpha 2_A$ adrenergic	human recombinant (RBL cells)	agonist	Fluorimetry (RT)	intracellular [Ca2+]	EC_{50} ~24 nM
Histamine H4	human recombinant (HEK-293 cells)	(partial) agonist	Cellular dielectric spectroscopy (28°C)	Impedance	EC_{50} ~5μM
Somatostatin 4 sst4	human recombinant (CHO cells)	agonist	HTRF* (37°C)	cAMP	EC_{50} ~7μM

*Homogeneous Time Resolved Fluorescence

CLE-400 Shows Robust Efficacy in a Mice Chloroquine-induced Pruritus Model



Total scratching events over 15 min (0-15 min).

****P < 0.0001 compared to vehicle-treated group. N=7-8 per group. One-way ANOVA with Fisher's LSD test.

Positive control, U-50,488, was injected IP and is known to be a short-acting antipruritic agent (lasting for ~15 to 30 min)

Treatment	Group Size	Frequency of dosing	Dose Level	Route	Endpoints
CLE-400 Placebo	8 CD-1 mice (4 Males + 4 Females)	Once daily for 5 days prior to induction (Day 5), with the 5th application 30 min prior to chloroquine challenge**	Topical 75 µL/cm² over 2 cm² (total of 150 µL)	Dermal	On day 5: Number of scratching events recorded for 30 min post-chloroquine induction (0-30min, at 5-min bins) and scored in a blinded fashion
CLE-400 0.1%			Topical 75 µL/cm² over 2 cm² (total of 150 µL)		
CLE-400 0.33%					
CLE-400 1%					
Positive control U-50,488*		Single Dose on Day 5, 30 min prior to chloroquine challenge	3 mg/kg	IP	

*U-50,488, a kappa opioid receptor agonist, administered intraperitoneally 30 min prior to chloroquine, significantly attenuated scratching, confirming the validity of the model.

**Chloroquine (0.4 mg/animal) was injected subcutaneously into the right shoulder area at time 0 on Day 5

Topical application of CLE-400 significantly suppressed and almost completed blocked chloroquine-induced scratching behaviors at all dose levels

CLE-400: results and conclusions

- Detomidine has been confirmed to potently activate α2A adrenergic receptors *in vitro,* with additional modalities that might contribute to CLE-400 efficacy, presenting a possible multi-modal MOA
- Main and secondary targets of detomidine have been shown to be expressed in the skin, strengthening the proposition of local activity of CLE-400
- Topical administration of CLE-400 demonstrated robust pharmacological effect in a mouse model of pruritus
- CLE-400 is generally well tolerated locally and systematically in efficacy and safety/toxicology studies
- FIH SAD study was completed successfully, 3 doses tested. MAD study is ongoing

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