Cannabinoids and the Endocannabinoid System

What are Cannabinoids?

Cannabinoids are molecules found in the cannabis plant, *Cannabis sativa.* There are over 100 known cannabinoids. The two best known cannabinoids are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD).

In humans these molecules interact with receptors found in The Endocannabinoid System (ECS), a biological system that plays an important role in many physiological processes in the body that maintain the balance between our physical and mental health. ECS receptors are found in cells throughout the body including the brain and the peripheral nervous system and are key to regulating pain, mood, memory, sleep, appetite, and the immune response to cancer. Where this endocannabinoid / receptor balance becomes disrupted by disease, the aim is to restore its optimal function with medicines that mimic natural cannabinoids.

Developing cannabinoids for doctors to prescribe

Cannabis has been used in popular medicine for thousands of years and is well known for its analgesic effects. Research has found that the cannabis plant produces over 100 active phytocannabinoids (pCBs), through its flowers. The two best known cannabinoids are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is the compound that is primarily responsible for the psychoactive effects of cannabis.

Despite advances in cultivation techniques, the variability of the compositions of cannabis flowers from plants with different genetics or grown in different conditions creates unpredictable or contradictory clinical datasets. Therefore, despite the potential benefits, there is a need for a more predictable drug discovery and development process to provide the evidence that cannabinoid-based medicines can target receptors in the body safely, effectively and exclusively and do this the same way every time a patient takes a medicine.

In the drug discovery process at OCTP, we are focused on 3 types of cannabinoids targeting the ECS receptors:

- *Synthesized phytocannabinoids* where the cannabinoid found in the plant is chemically reproduced e.g. CBD, THC
- *Cannabinoid derivatives* where the compounds are chemically modified to improve drug-like characteristics
- *Novel chemical entities* (NCEs) - these are not cannabinoids but are chemically synthesized to behave like them and interact with cannabinoid receptors

It is expected that each compound developed by OCTP will serve to resolve, not just one, but several severe conditions including some rare conditions.

Cannabinoids in pain medicine

OCTP is largely focused on developing medicines to treat chronic pain conditions. Current pain treatments consist predominantly of opioids, anti-inflammatory, anti-convulsant and anti-depressant drugs. Many of the medicines used to treat pain are not licensed in pain. Many millions of people are living with chronic pain every day that is either unresolved by or is resistant to these current treatments, leaving many of them dependent on opioids and the consequences of these. In the US alone, this number is estimated to be 50 million with 60,000 opioid-related deaths in the US in 2020. There is an urgent need for new, effective and non-addictive treatments and regulatory agencies are supporting efforts to address this crisis.

Pre-clinical data and a small number of clinical trials in acute, neuropathic, chronic and cancer pain models suggest that receptors of the endocannabinoid system (ECS) play an important role in processing pain and that modulation of the ECS can alleviate pain. The most studied and prominent ECS receptors are CB1 and CB2.

Through medicinal chemistry and screening, cannabinoids can be designed to target single or multiple receptors. OCTP is actively working with four drug development programmes. Its lead drug candidate, OCT461201, for example, is highly selective for CB2 receptors in the nerves and immune cells that contribute to controlling the pain response. It is being developed, with an initial target indication of Chemotherapy-Induced Peripheral Neuropathy (CIPN). An estimated 60% of people undergoing chemotherapy are affected by CIPN after 3 months. The hallmarks of CIPN are pain, numbness and tingling in the extremities. CIPN can be progressive, enduring, often irreversible, leading to many years of debilitation and suffering. Following successful pre-clinical studies, OCT461201 is currently in Phase I.

OCTP's second compound, OCT130401 combines two different cannabinoids (THC and CBD) which are known for their analgesic and anti-inflammatory properties and will target both CB1 and CB2. The combination aims to provide both immediate pain relief and long-term amelioration for painful conditions where inflammation also plays a role. It too is ready for human trials and will be initially targeting a rare and severe type of face pain, called Trigeminal Neuralgia. This condition causes debilitating and excruciating pain, has a fast and unexpected onset and because of this has been difficult to treat. Sufferers experience an intense, stabbing electric shock-like pain. Each episode may only last few seconds or minutes, but some people will suffer multiple (up to 100) episodes in one day. OCT130401 will be designated orphan status and delivered via an inhaler which may mean faster onset of pain relief when compared to other routes. Cases are increasing with between approximately 10,000 and 15,000 new cases in the United States diagnosed each year. OCTP estimates that in 2021 there were more than 77,000 people living with the condition in the UK.

Programmes 3 & 4 are in early stage development and have significantly advanced as a result of OCTP's worldwide exclusive licence from Canopy Growth Corporation which includes 335 cannabinoid derivatives, already available and tested together with 14 patent families.

Programme 3 (OCT960609) is targeting an as yet undisclosed indication the pain market. It is a dual CB1/CB2 agonist which, in early studies, has demonstrated good bioavailability via oral administration as well as a better profile than THC in terms of analgesia and behavioural alterations.

Programme 4 marks an expansion of OCTP's strategy as this molecule is targeting oncology, rather than pain. Programme 4 is a potential 'first in class' immunotherapy agent for the treatment of solid tumours. Analysis of the initial data shows excellent drug-like potential in terms of *in vitro* potency and selectivity to target, as well as *in vivo* availability in blood. This implies substantive potential for the development of a cannabinoid-based medicine that could be taken at home as a tablet.

The Company has built a library of nearly 500 cannabinoid compounds which will allow it to develop further medicines to treat unmet needs not just in chronic pain and cancer, but potentially in other therapeutic areas such as epilepsy.

For further information or to read the Company presentation, please visit the website www.oxcantech.com

ENDS

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