The CGRP story and its role in migraine pathophysiology.

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Migraine is a painful, debilitating neurological disorder that manifests as a debilitating headache associated with altered sensory perception, having a huge impact on individual and public health. In a survey about years lived with disability, migraine was ranked on the third place. Although evidence suggest no increase in migraine prevalence in a ten year period, the cumulative lifetime incidence is very high (43% in women, 18% in men), affecting especially young adults.

Great progress has been made in understanding the pathophysiology of migraine. However, there are still some questions regarding the origin of migraine pain and on its chronification. The neuropeptide calcitonin gene-related peptide (CGRP) is now firmly established as a key player in migraine. The first evidence was presented already 1984, showing that sensory nerves on cerebral arteries store calcitonin gene-related peptide (CGRP) using immunohistochemistry, performed surgical denervation and quantification of CGRP, did *in vivo* work and defined the trigeminovascular reflex with CGRP as the main molecule.

In 1988, we observed upon operation of patients with trigeminal neuralgia that CGRP was released into the jugular venous blood and at the same time there was unilateral flushing. This was the start of our migraine project. CGRP was found to be released in acute migraine and cluster headache attacks and correlated with the pain, and that both pain and increased CGRP levels were aborted by a triptan. Thus, CGRP is a key molecule in primary headache disorders. Subsequent work provided a wealth of preclinical and clinical data in support (Ho et al, Nature Rev Neurol 2010).

Industry picked up the idea and started developed CGRP blockers 10-15 years ago. After the first proof-of-concept study (2004) several trials using small molecules that could be given orally, revealed positive effects both in acute migraine attacks and in a prophylaxis study with gepants (Edvinsson & Linde, Lancet Neurol 2010). Due to liver toxicity this program was

halted. However today this has been followed by 4 different companies using antibodies towards CGRP or the CGRP receptor and they have revealed positive results in phase 2 trials. It is expected that CGRP blockers may reach the market in about 2-3 years. The preliminary data show compared to placebo no significant side effects and good efficacy. Despite this progress in the clinical arena, the details of the mechanisms and involvement of CGRP in migraine pathophysiology remain unclear providing room for further research.