

Anti-CGRP therapies: similar but not the same

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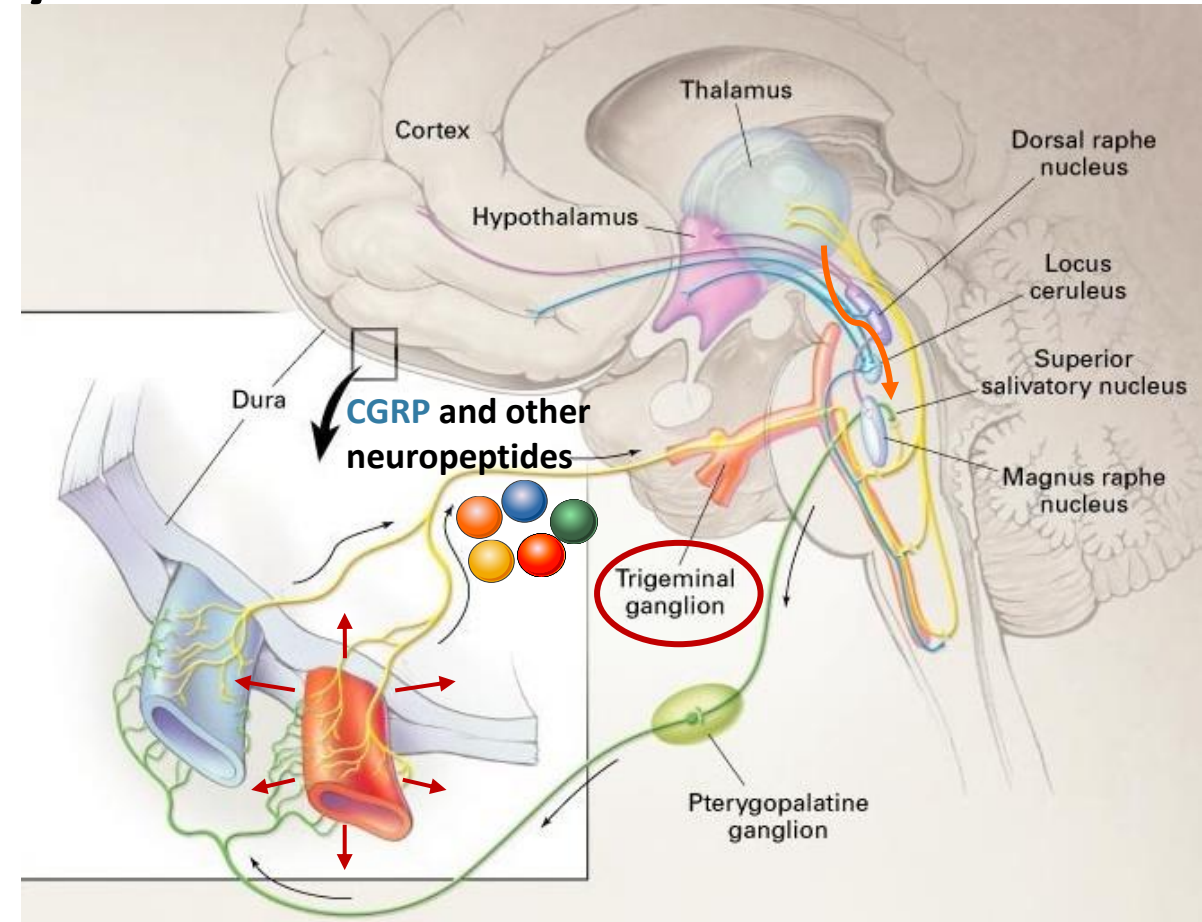
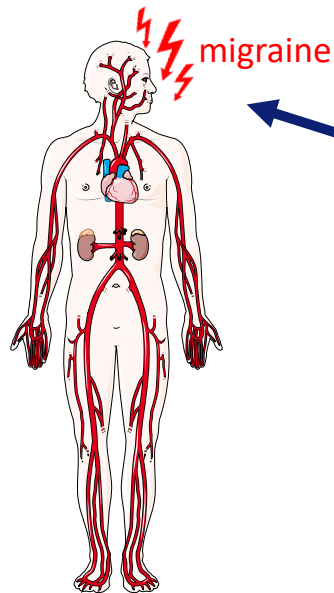
Disclosures

Research grants/Consulting/speaker fee	Allergan/Abbvie, Amgen/Novartis, Eli Lilly, Manistee, Pfizer, Satsuma, Teva, Tonix
Board/Chair	President European Headache Federation Board member Dutch Headache Society



Migraine pathophysiology

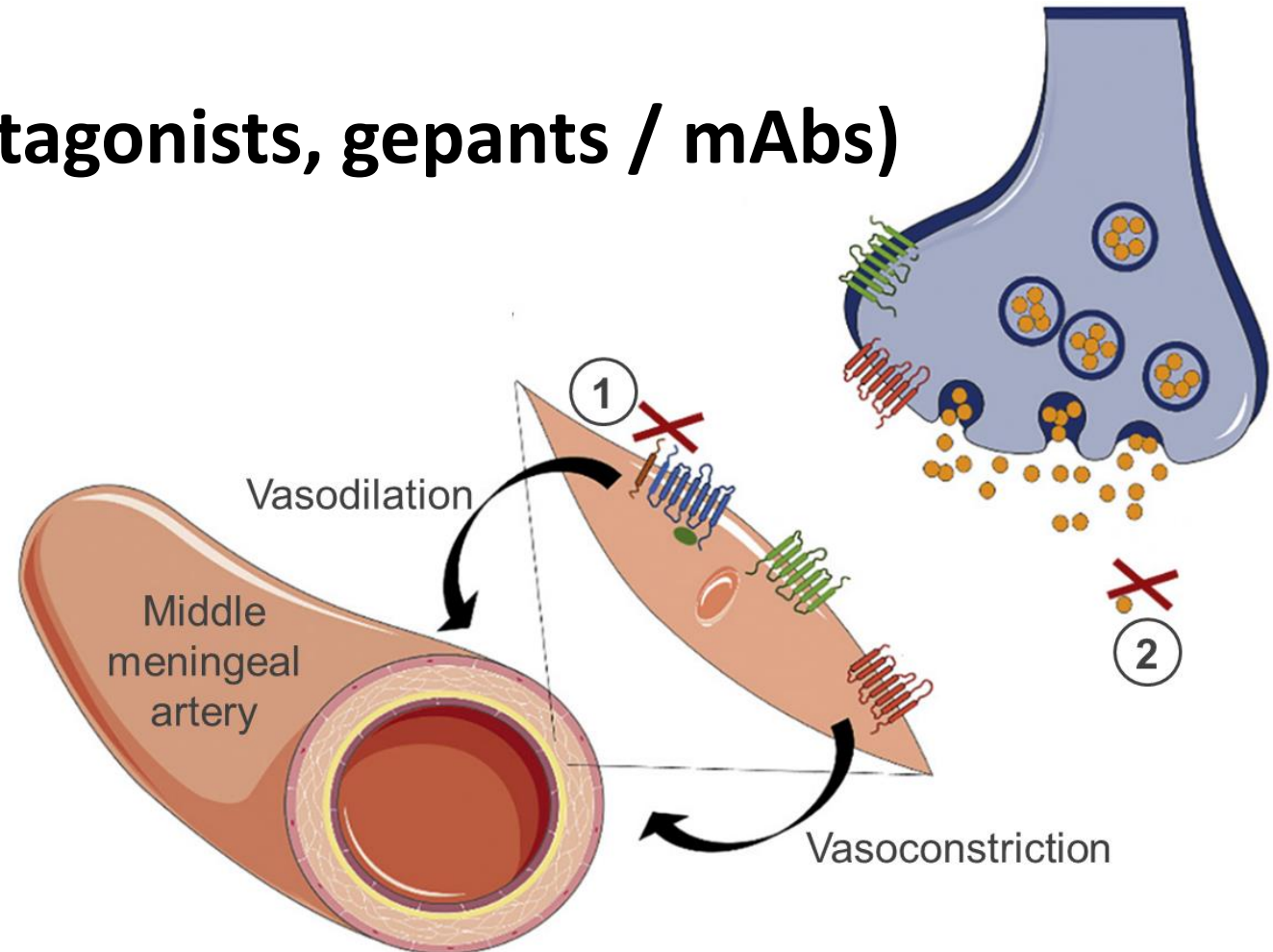
- Exact cause yet unknown
- Activation of the trigeminovascular system:
 - Trigeminal nerve activation
 - Neuropeptide release (**CGRP**)
 - Vasodilation
 - Activation of nociceptors



Calcitonin Gene-Related Peptide blockade:

1) **Receptor** (small molecule antagonists, gepants / mAbs)

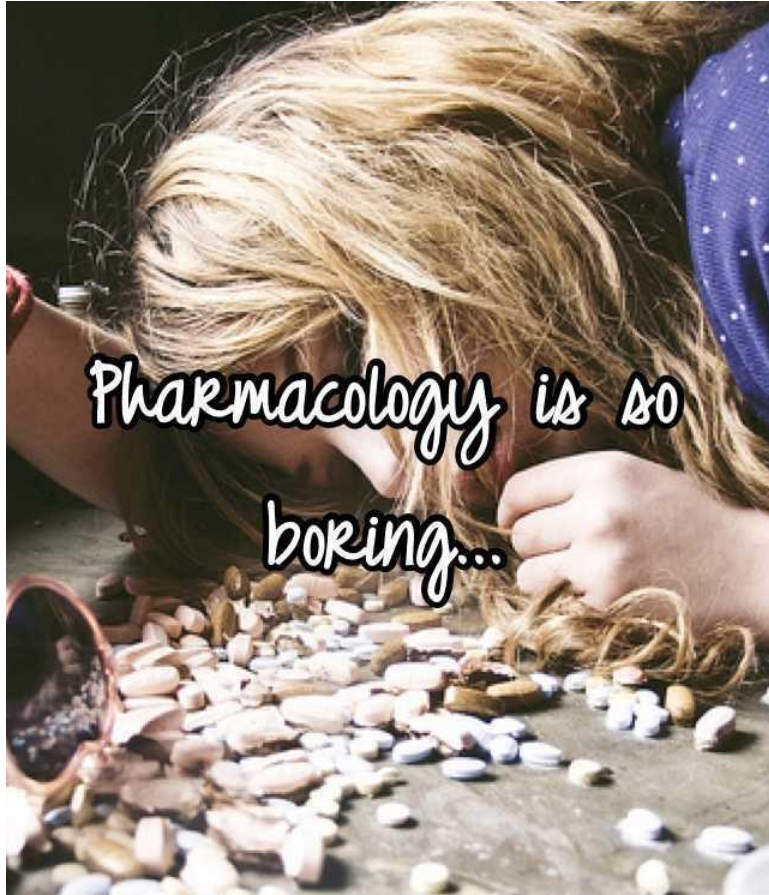
2) **Ligand** (mAbs)



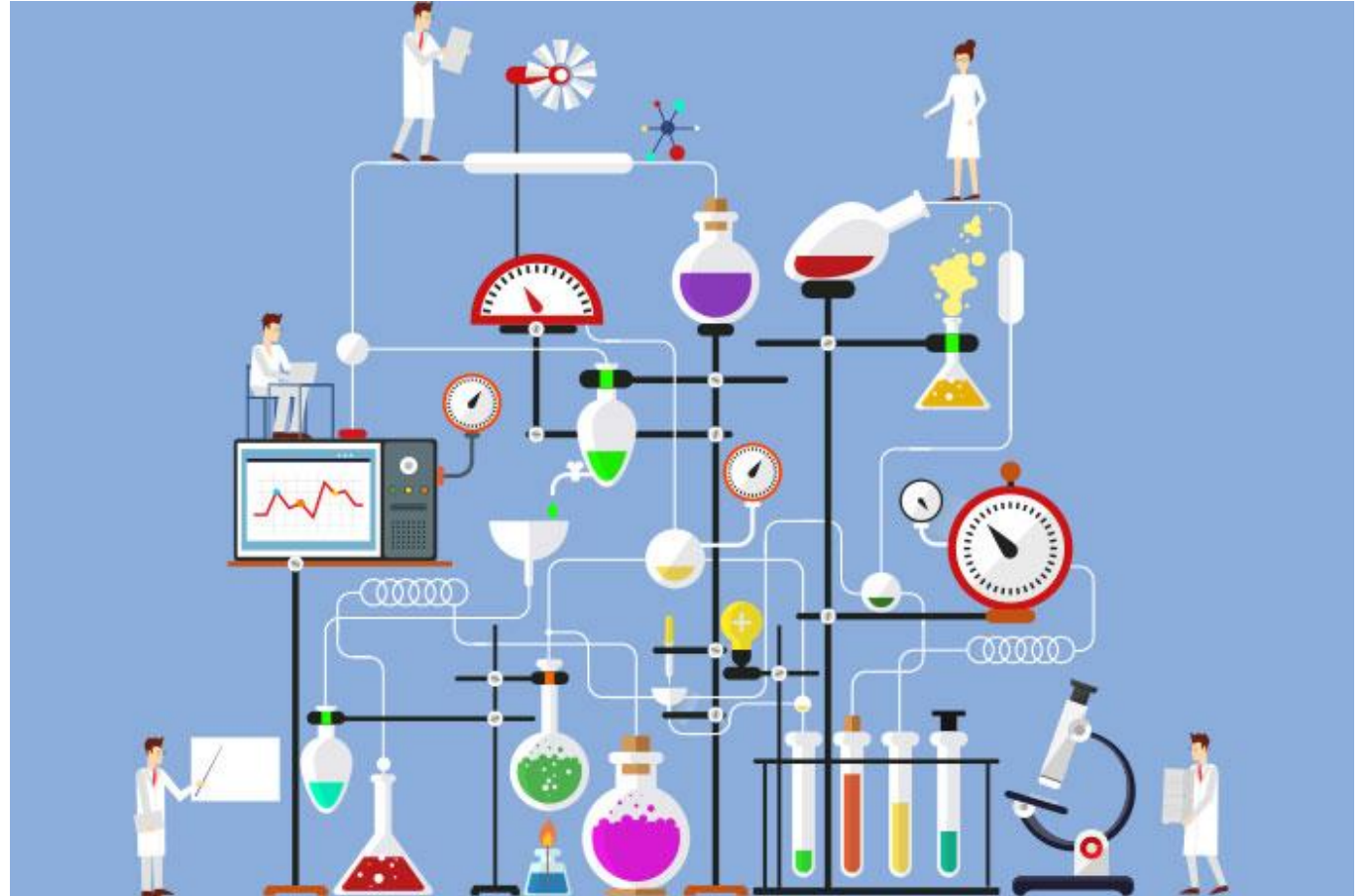
mAb, monoclonal antibody

de Vries T, Villalón CM, Maassen van den Brink A. Pharmacol Ther 2020.

What is the pharmacological mechanism of action of the gepants and mAbs?



Pharmacology is boring...



Pharmacology is complicated...



***Pharmacology is interesting,
important and clinically relevant!***



What is the importance of different plasma half lives for various drugs?

Pregnancy wish

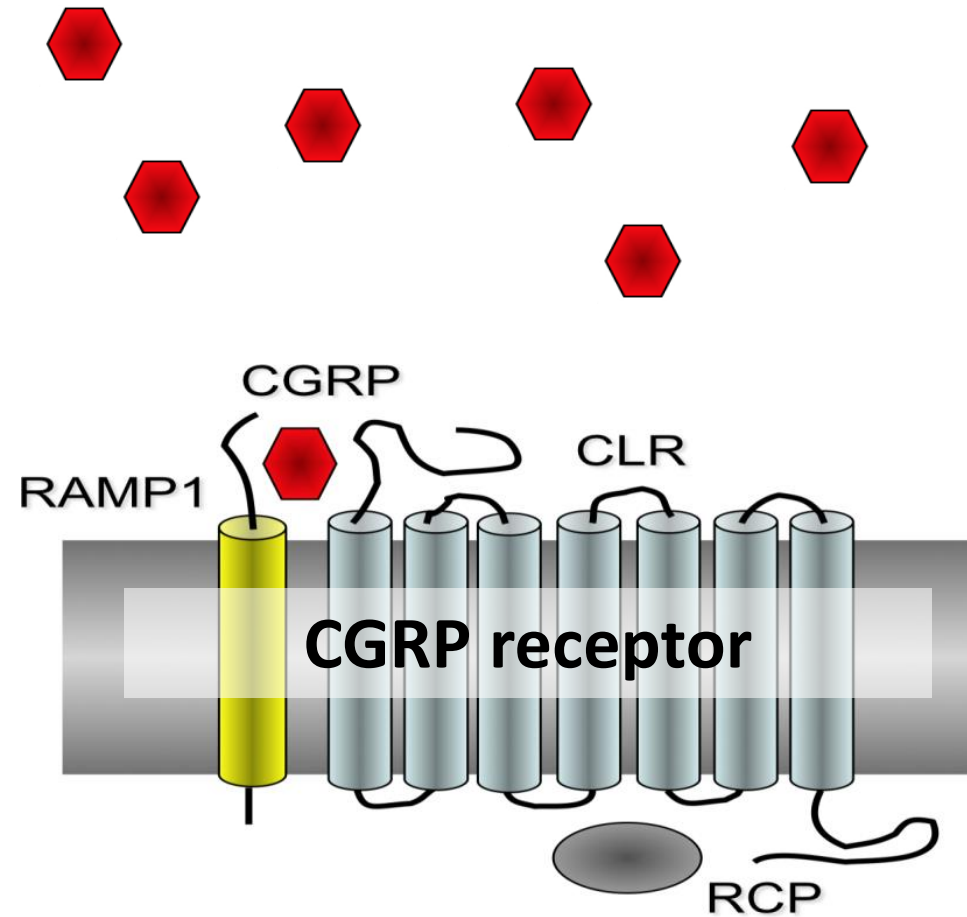


- **Migraine most prevalent in young women**
- **Plasma half life gepants: ca 5-11 hr**
- **Plasma half life mAbs: ca 4 weeks**
- **Before drug disappears from the body: $5 \times T_{1/2}$**
 - gepants: ca 1-2 days**
 - mAbs: ca 5 months**

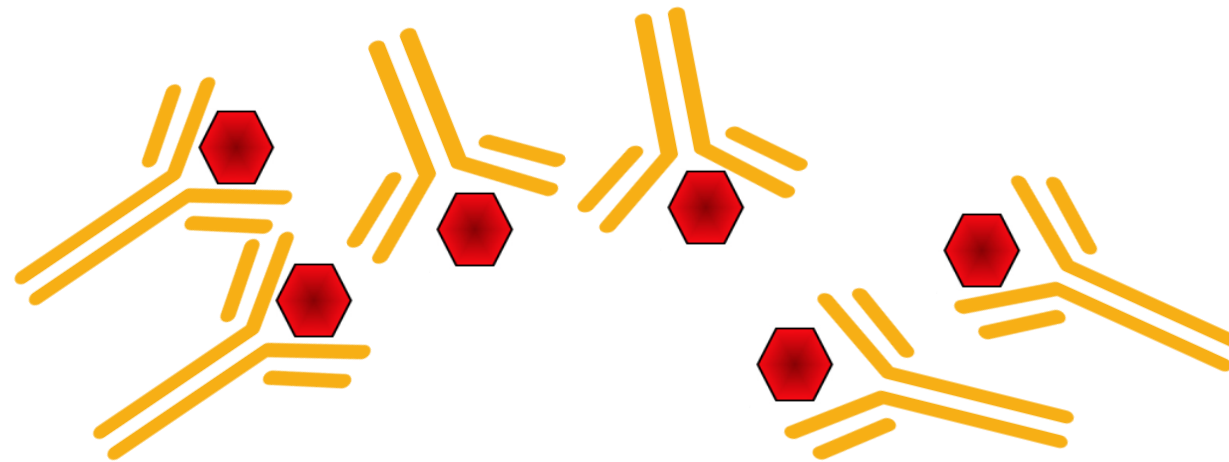


**Does it matter whether the peptide
or its receptor is blocked?**

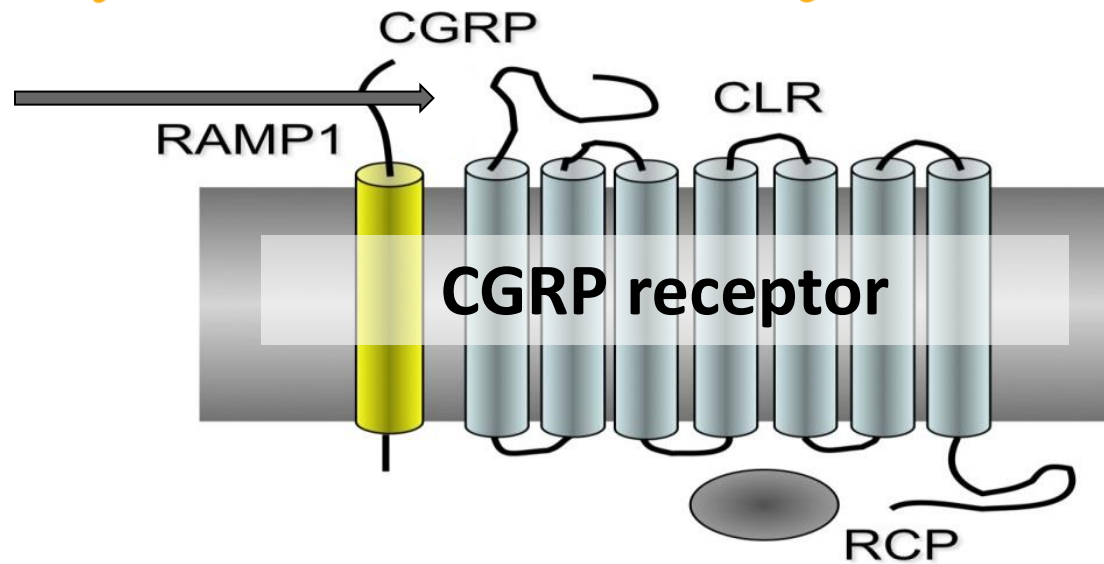
Antibodies against CGRP or the CGRP receptor



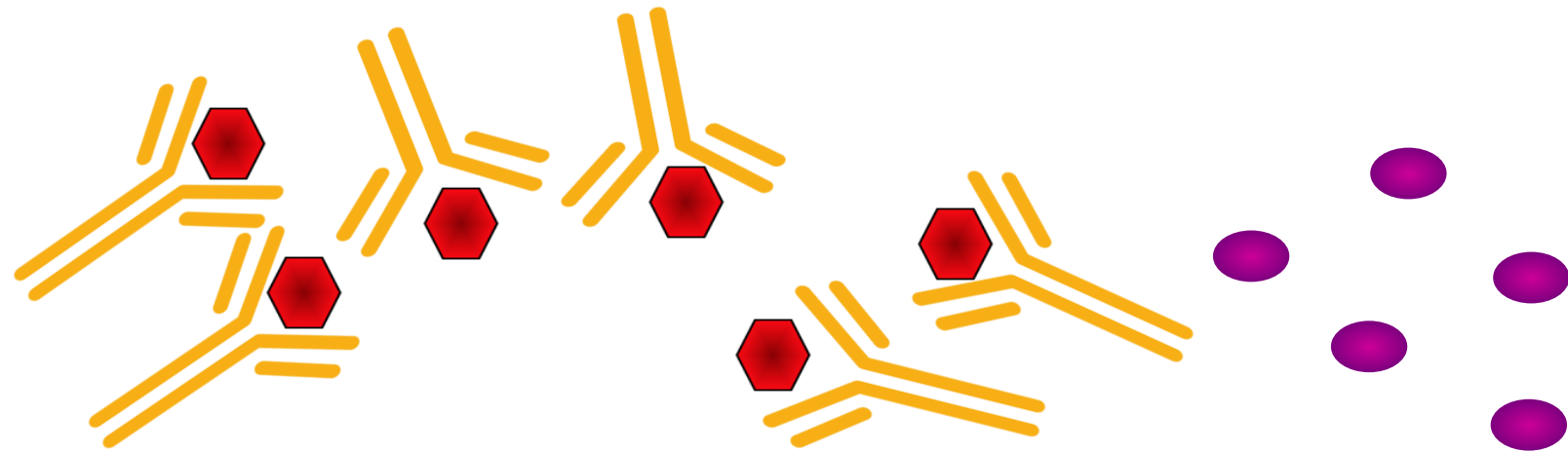
Antibodies against CGRP



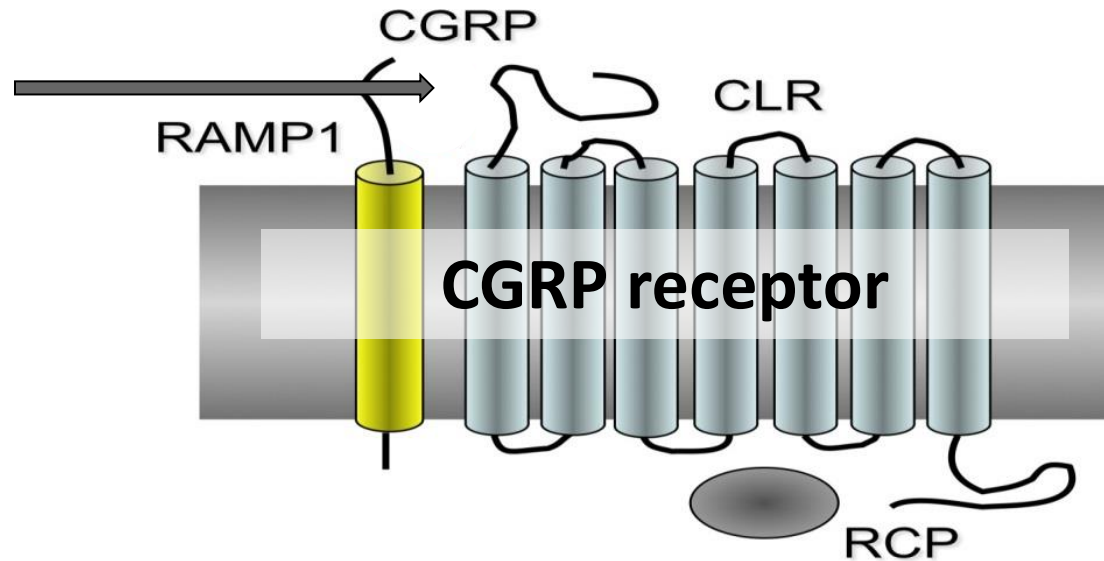
No CGRP available for binding to its receptor



Antibodies against CGRP

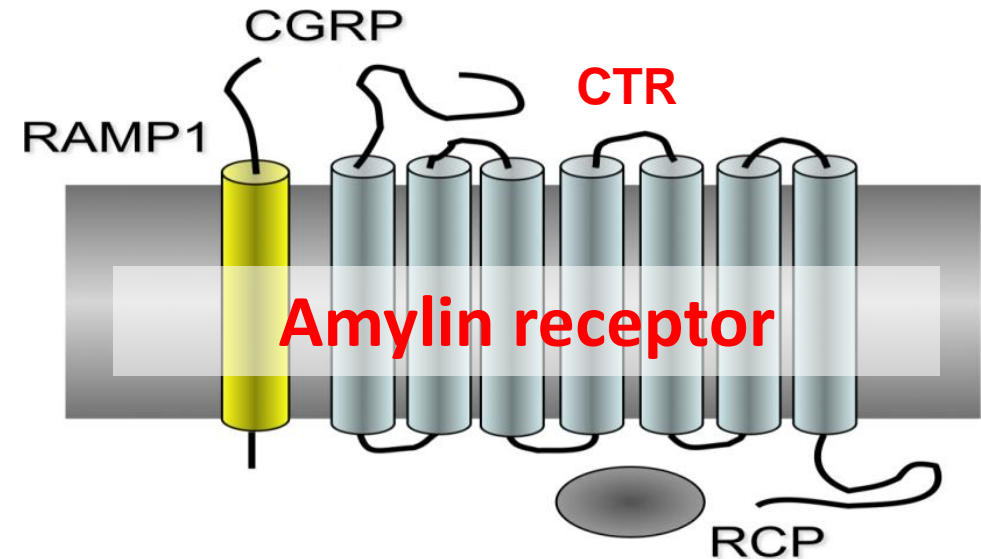
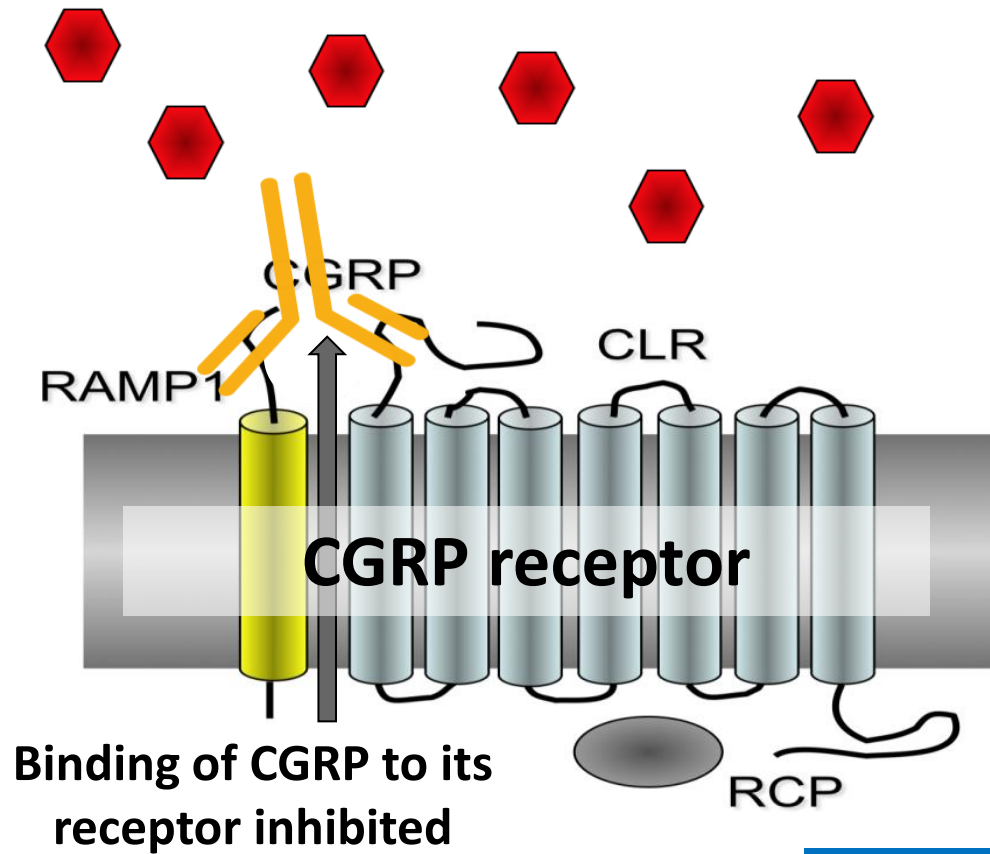


No CGRP available for binding to its receptor



Relevant when other peptides available

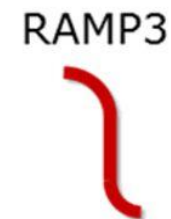
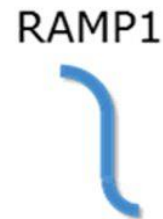
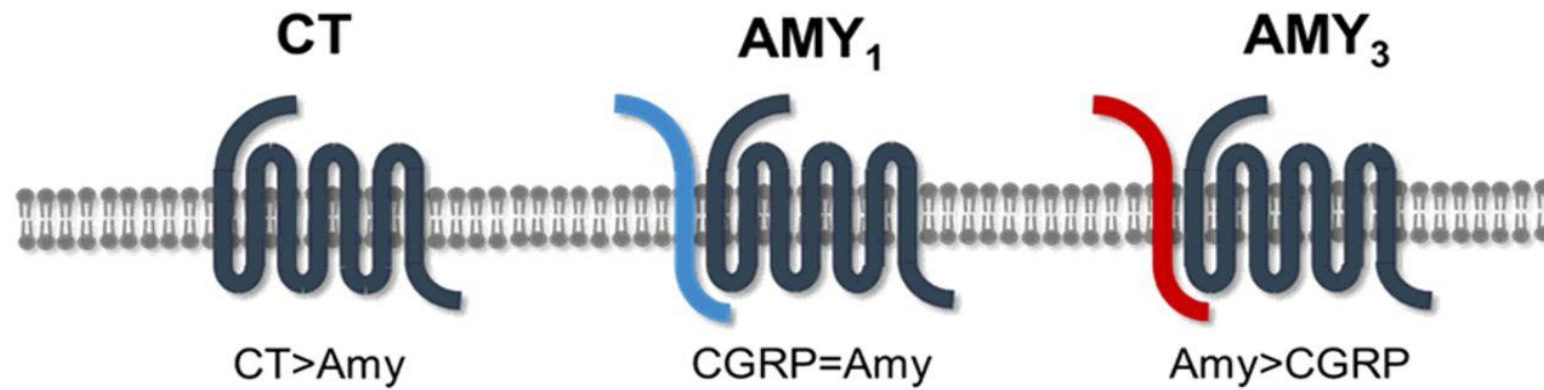
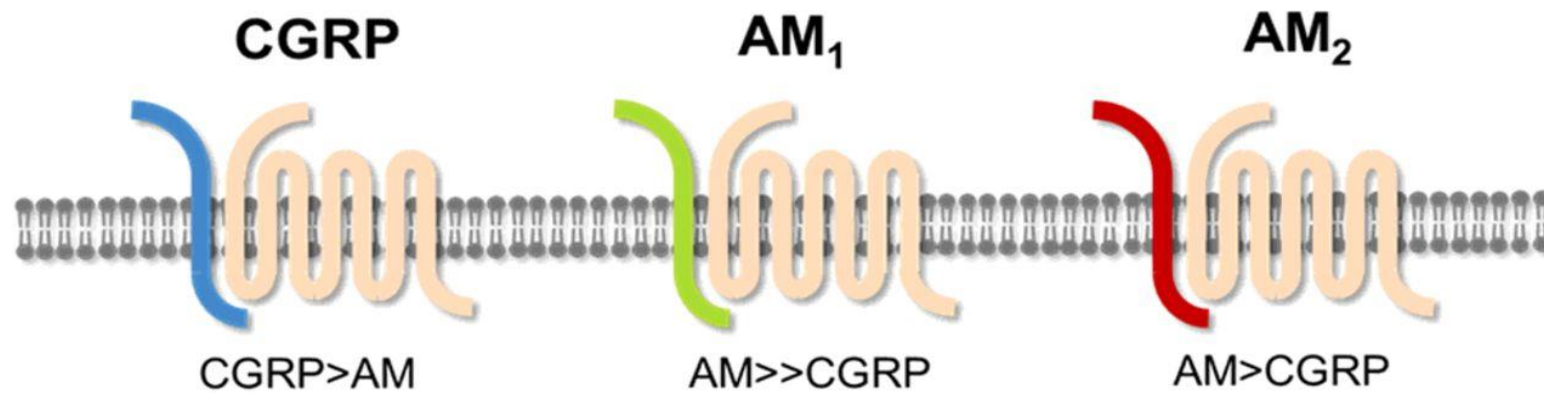
Antibody / antagonist against the CGRP receptor



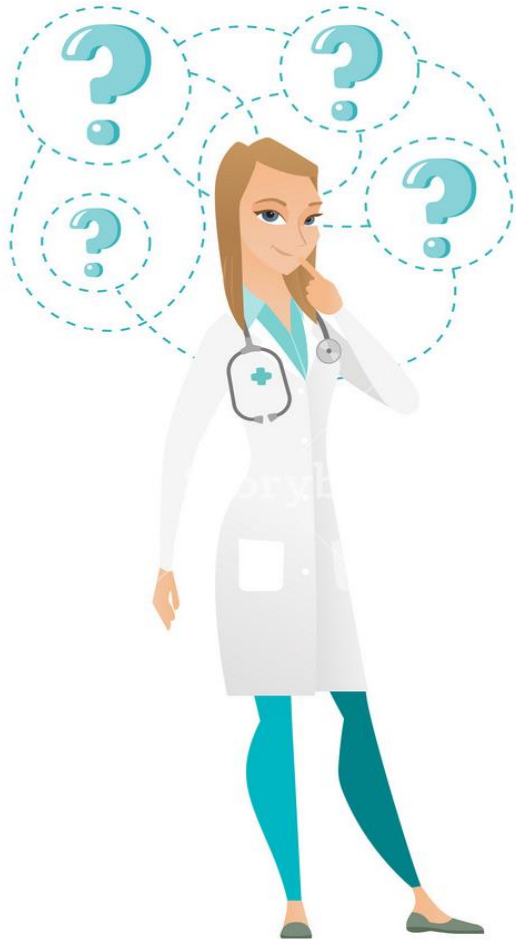
Relevant when other receptors available

CTR, calcitonin receptor

Maassen Van Den Brink A, et al. Trends Pharma Sci 2016;37:779-88



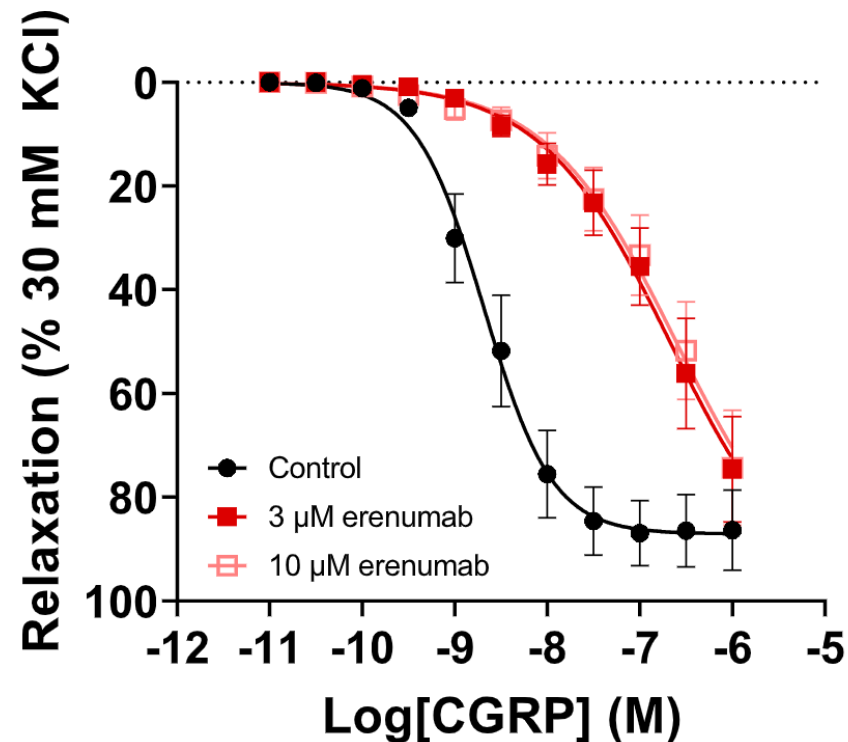
Another clinical question:



Does it make sense to use a gepant as attack treatment while using anti-CGRP receptor prophylaxis?

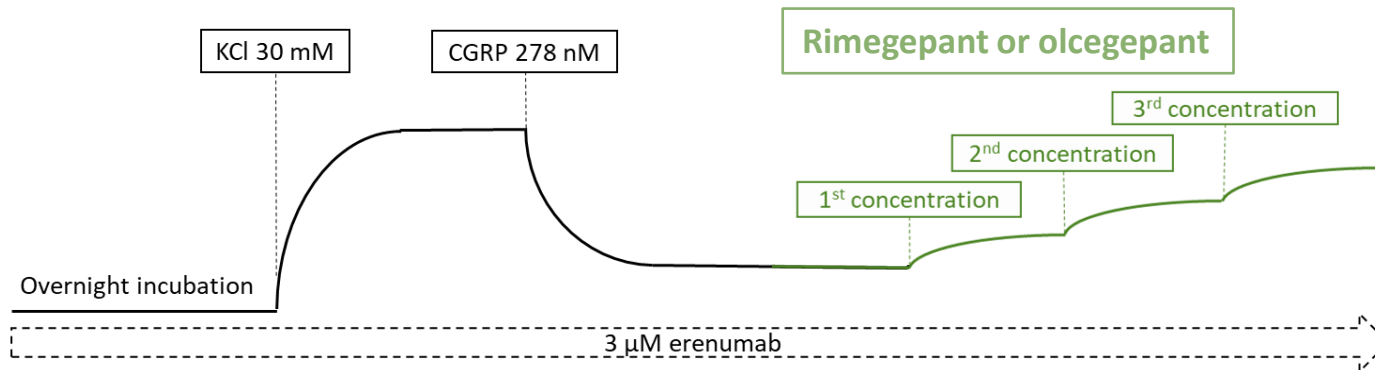
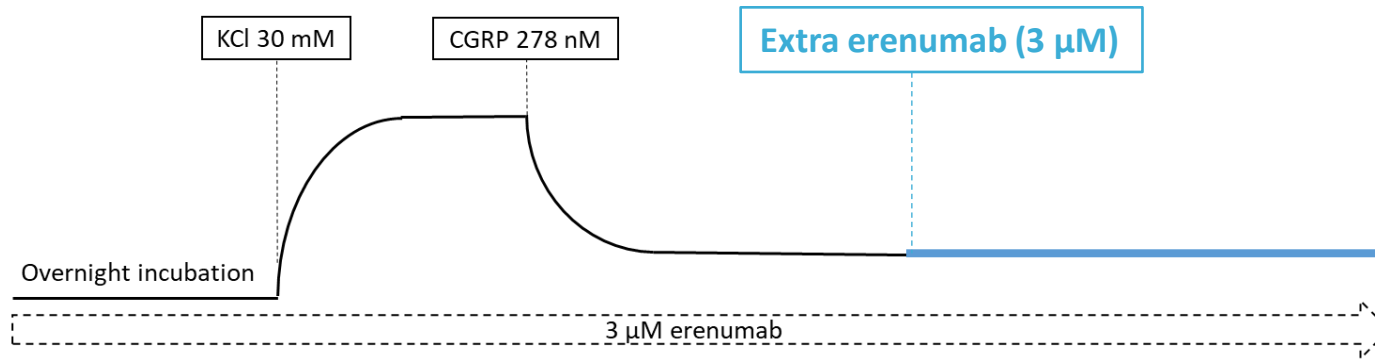
Maximum shift after erenumab

- Which concentration of erenumab causes a maximum effect on CGRP-induced relaxation of human coronary arteries?



→ 3 μM erenumab induces a maximum shift in the concentration-response curve to CGRP

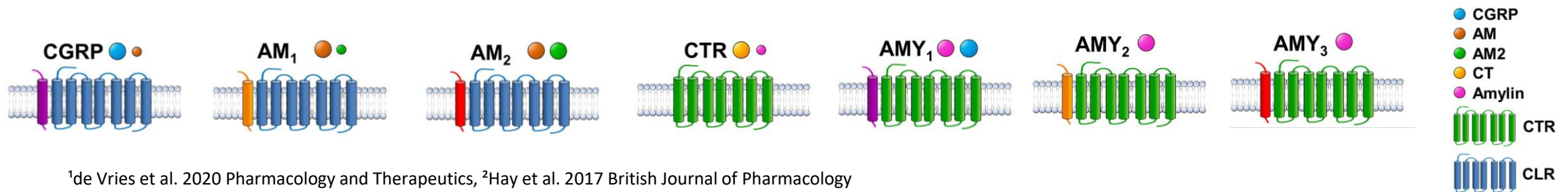
Gepants in the presence of erenumab



Olcegepant not approved in EU

On top of 3 μM erenumab

- Gepants (rimegepant, olcegepant) induced additional inhibition of the CGRP response
- Unexpected results: theoretically target the same receptor: CLR/RAMP1



¹de Vries et al. 2020 Pharmacology and Therapeutics, ²Hay et al. 2017 British Journal of Pharmacology

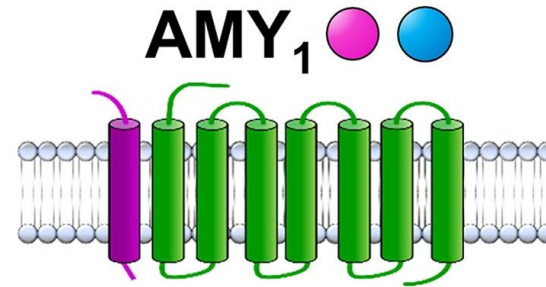
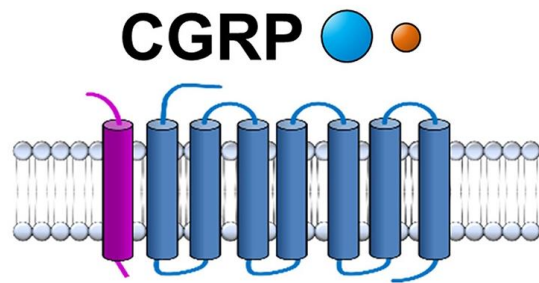
Olcegepant not approved in EU

De Vries et al., Br J Pharmacol 2024

How could this be explained?

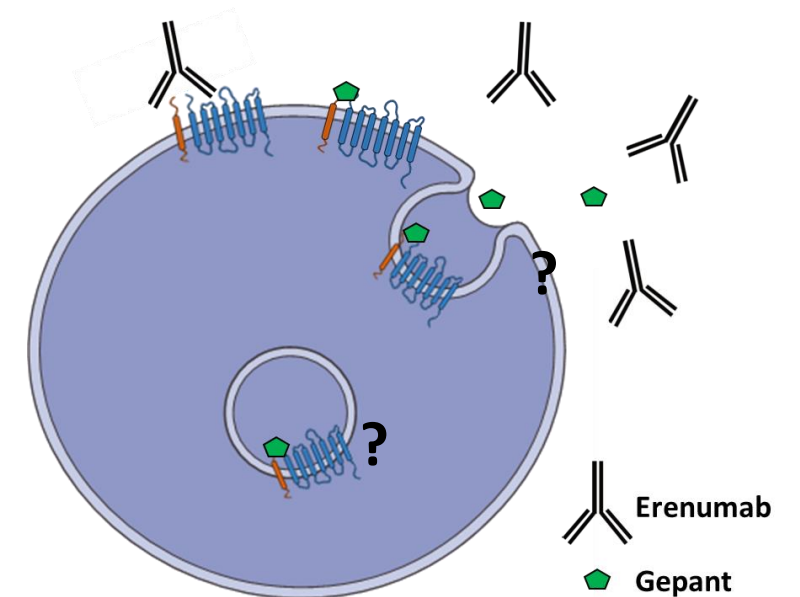
The mechanism of action of erenumab and gepants may not be identical:

- Targeting different receptors

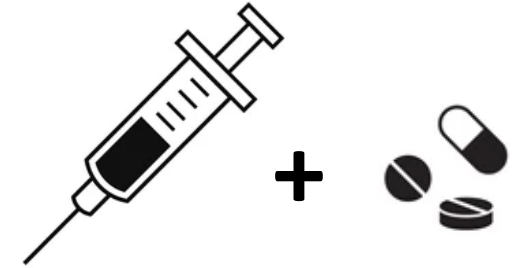


- Receptor internalization

More research into these mechanisms is needed!



Clinical relevance; combining treatment with erenumab with gepants



- Based on in vitro pharmacological experiments...
- Patients using erenumab could benefit from gepants as acute treatment
- Combining treatment with erenumab with gepants: up to now favourable clinical data^{1,2}, but only few and short term studies

More research into cardiovascular safety is needed!



What is the importance of route of administration for the gepants?

RESEARCH

Open Access



Comparison of gepant effects at therapeutic plasma concentrations: connecting pharmacodynamics and pharmacokinetics

Deirdre M. Boucherie¹, Ruben Dammers², Arnaud Vincent², A. H. Jan Danser¹ and Antoinette MaassenVanDenBrink^{1*}

Comment by Uwe Reuter



The improvement after 2 h for a multitude of endpoints is similar to that of the oral CGRP receptor antagonists rimegepant and ubrogepant, which is to be expected as these drugs share the same mechanism of action as zavegepant.^{3,4}

Articles

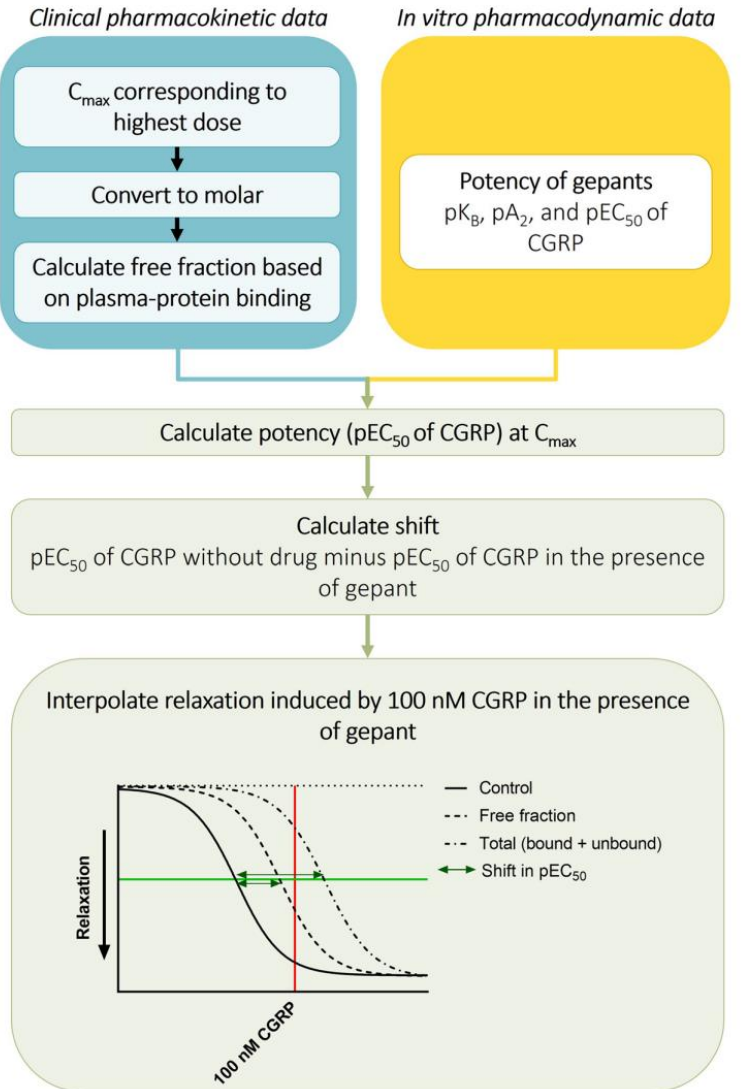
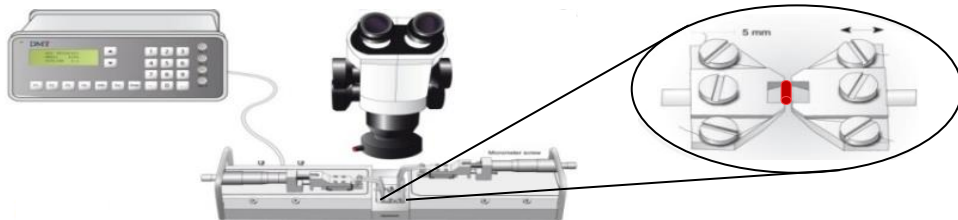
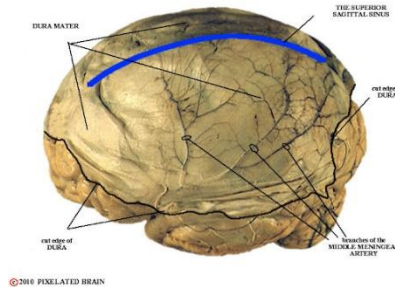
Safety, tolerability, and efficacy of zavegepant 10 mg nasal spray for the acute treatment of migraine in the USA: a phase 3, double-blind, randomised, placebo-controlled multicentre trial



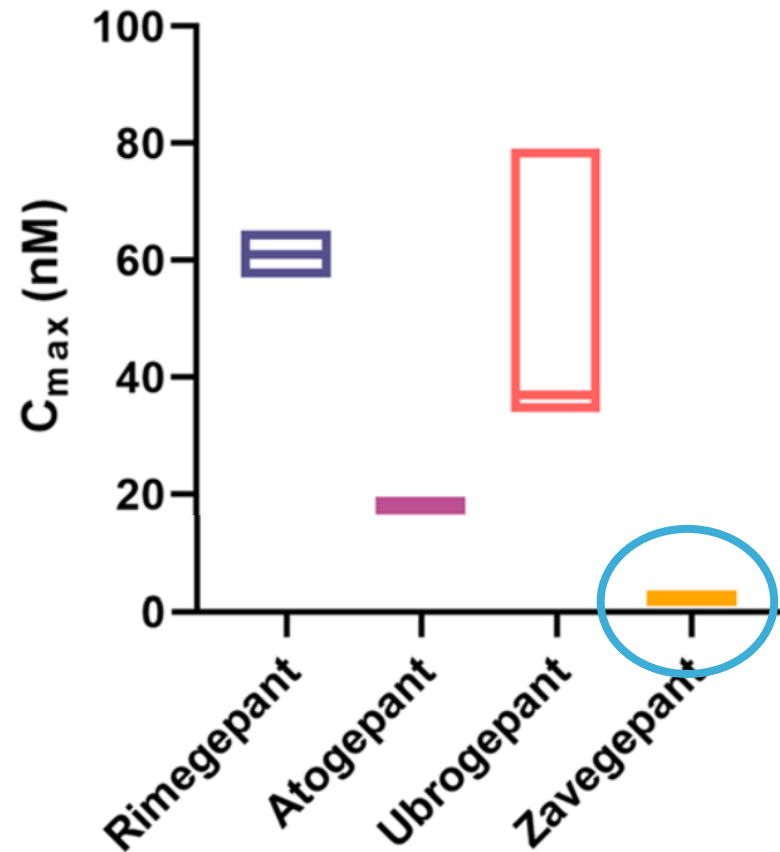
Richard B Lipton, Robert Croop, David A Stock, Jennifer Madonia, Micaela Forshaw, Meghan Lovegren, Linda Mosher, Vladimir Coric, Peter J Goadsby

Human middle meningeal artery

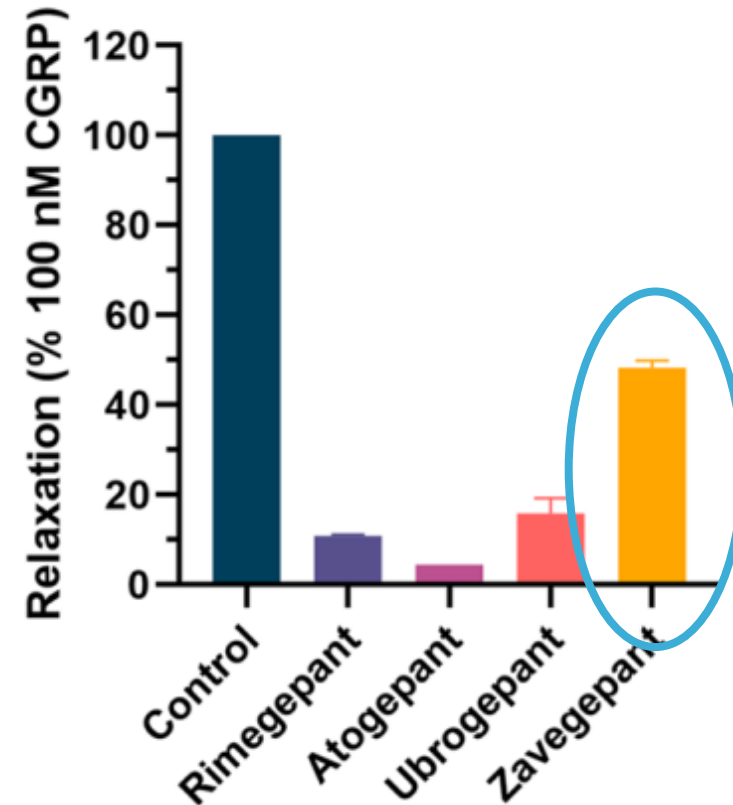
Assuming similar efficacy across the gepants



Clinical data*



Combined with lab data*

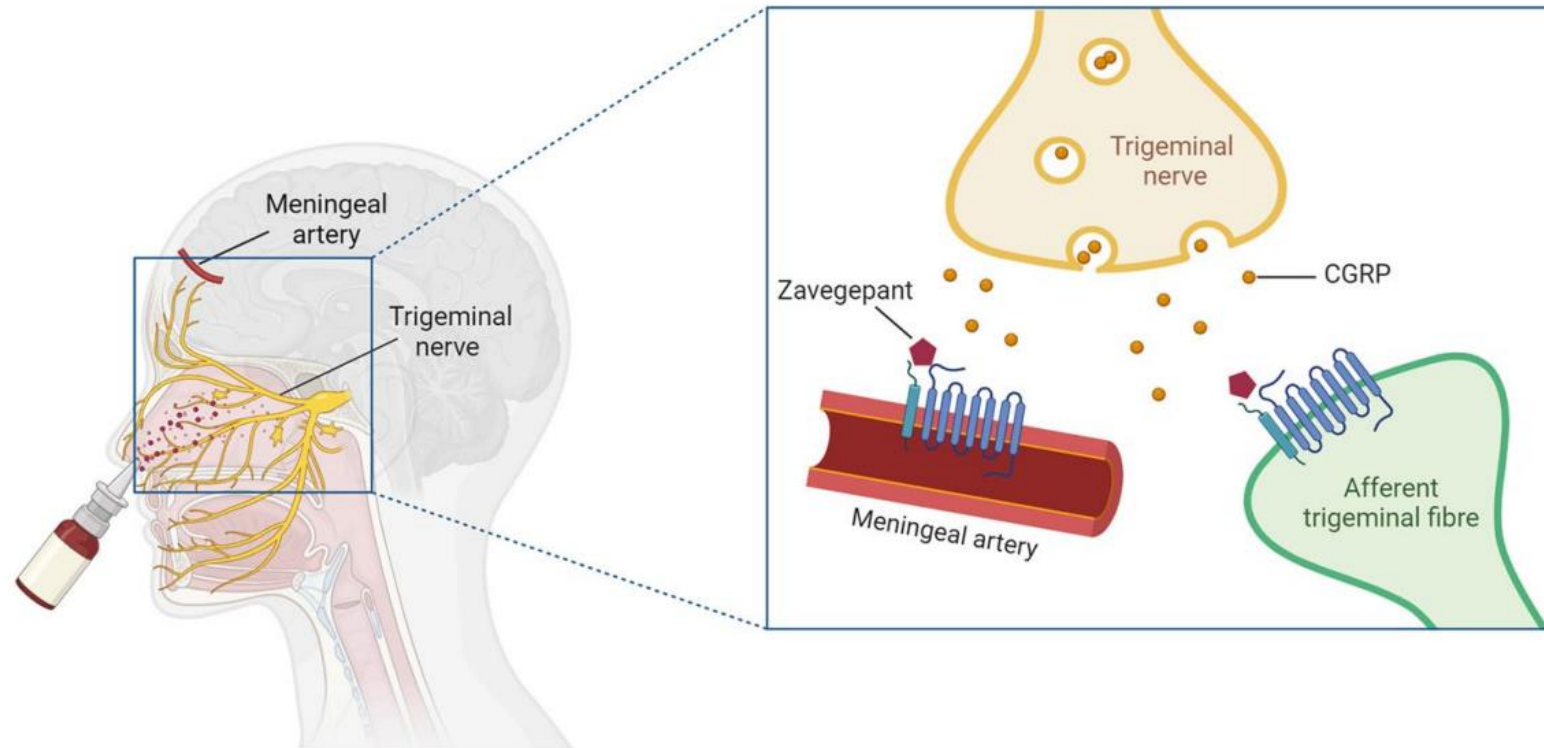


Ubrogepant and zavegepant not approved in EU

Based on systemic plasma levels, zavegepant would have been expected to be less effective than other gepants, but is equi-effective

*) similar conclusions with or without correction for plasma protein binding

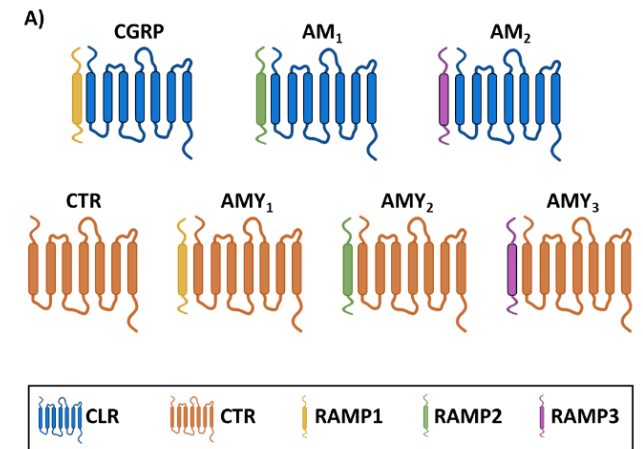
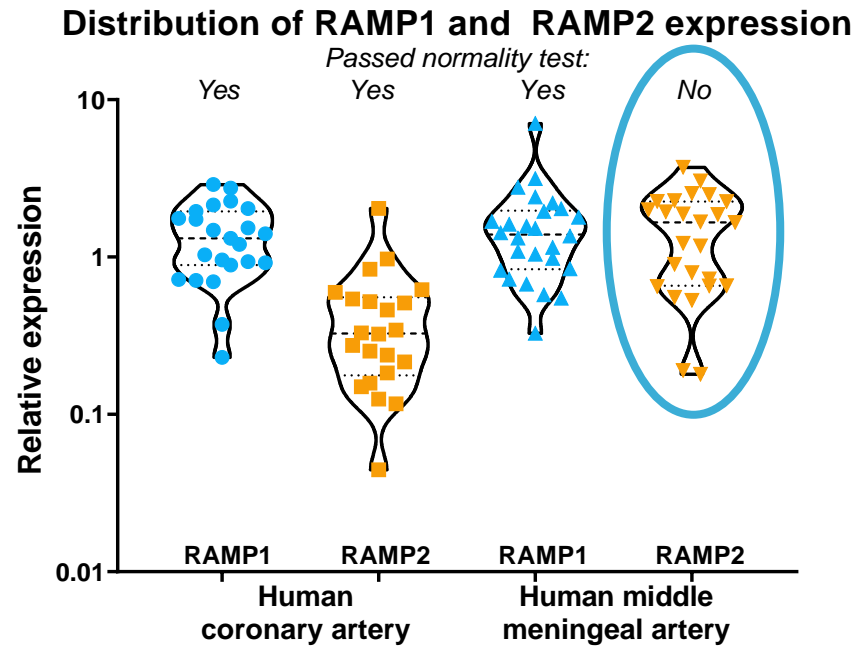
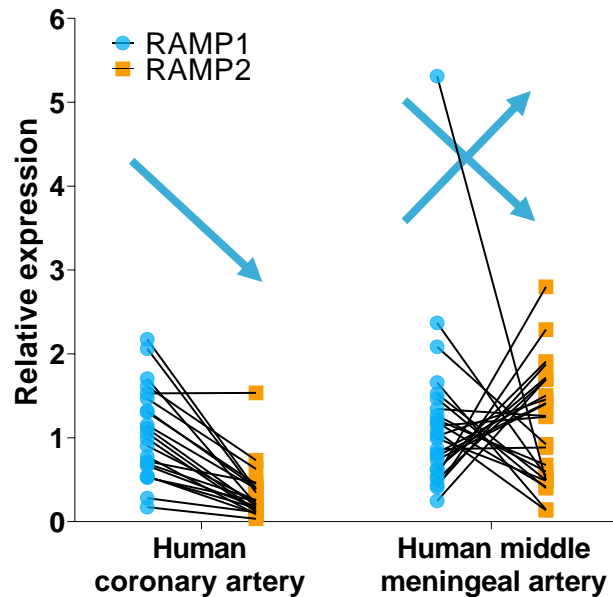
Does nasal administration of zavegepant have direct trigeminovascular effects?



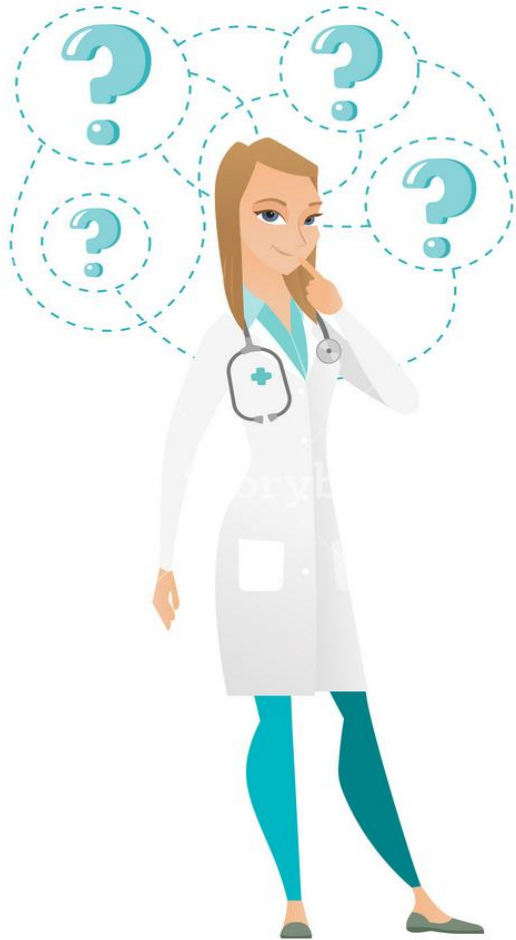


Besides differences between drugs, are there relevant pharmacodynamic differences between patients?

CGRP receptors, but also AM receptors in the trigeminovascular system



Is there a subpopulation of patients where in the trigeminovascular system adrenomedullin receptors are also relevant besides CGRP receptors?
Consequences for drug response?



For CGRP-binding antibodies, but also for CGRP receptor antagonists, does it matter whether a response is elicited by α CGRP or β CGRP?

EHC, poster presentation by Deirdre Boucherie



18th European
Headache Congress

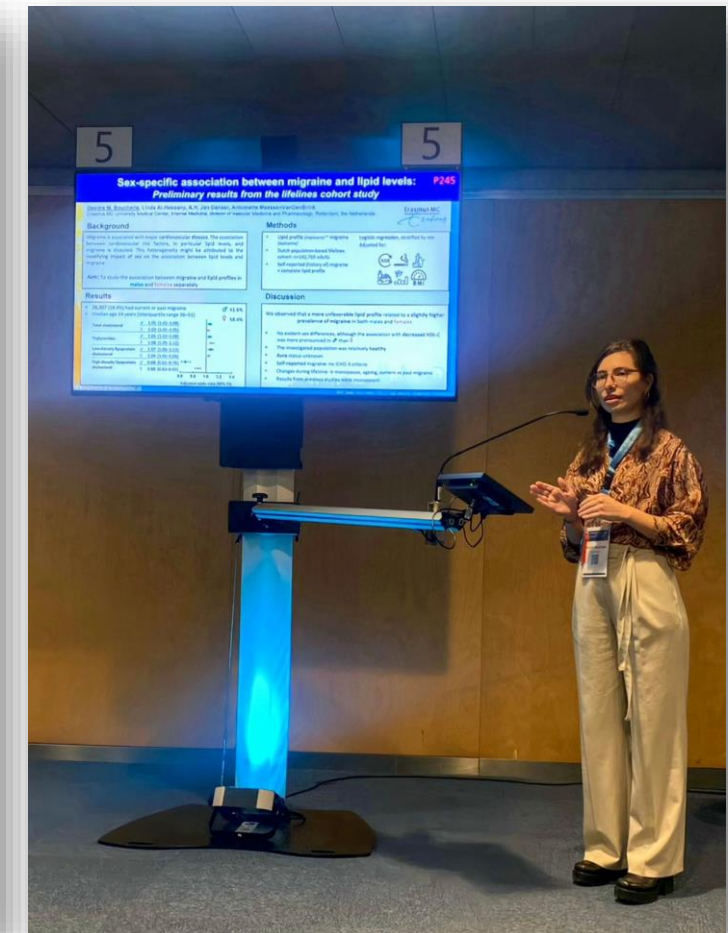
Towards a better headache treatment
for everyone

4–7 December 2024
Rotterdam (The Netherlands)

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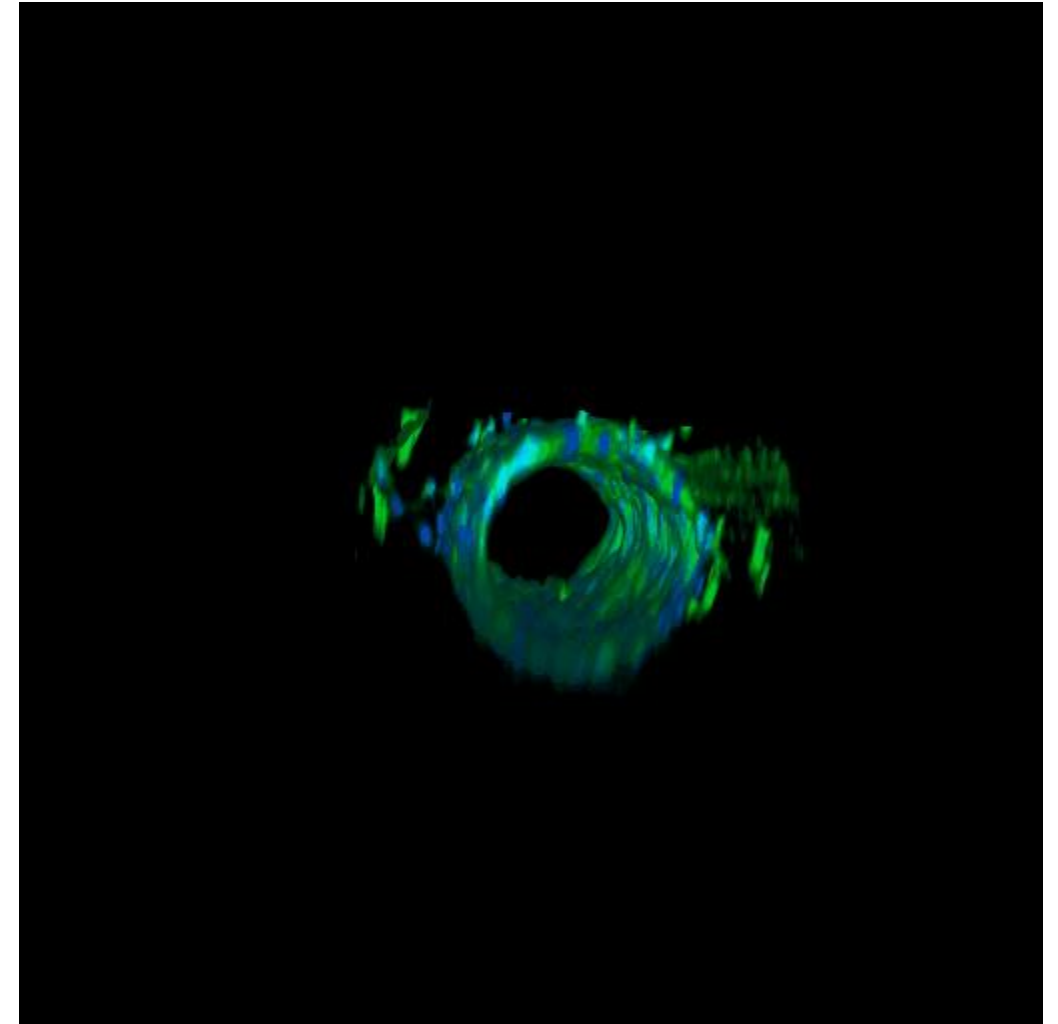
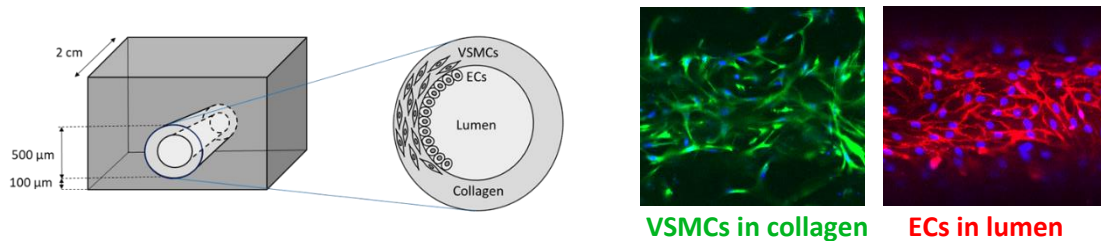
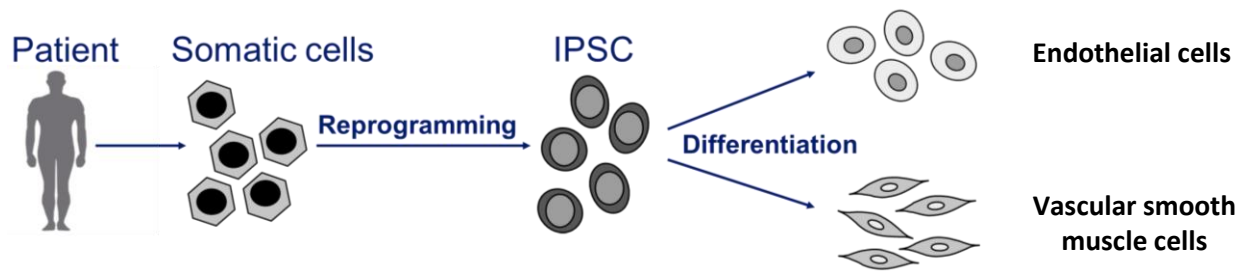


And what should we do in future?



**Always combine clinical
and basic science!**

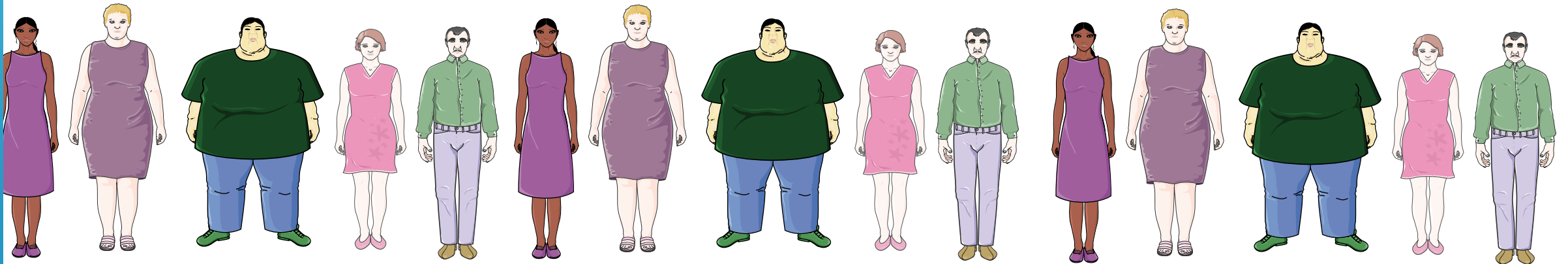
Development of vessel-on-chip



Allows detailed pharmacological studies on specific patients

Conclusions

- Pharmacological knowledge can help the clinician
- Translational thinking, combining clinical questions with basic science, will improve science as well as patient care





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