

Part 1: Project proposal

SPARK DENMARK

Project title:	Non-opioid pain relief through a novel target
Applicant:	Walden Emil Bjørn-Yoshimoto
Institution:	University of Copenhagen
Department:	Department of Biomedical Sciences
Additional team members:	Helena Safavi; Sara Hestehave

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A. Description of the unmet need

While about 1 in 5 people suffer from chronic pain, current pharmacological interventions are ill-suited to treat the majority of these. The most effective drugs are opioids. They are of course addictive but are also less effective for chronic treatment due to their tendency to “desensitize” their receptors, thereby decreasing efficaciousness over time. For some pain indications there are alternatives, but they present problems of their own. The most widely used non-opioid pain drugs include non-steroid anti-inflammatory drugs (NSAIDs), anticonvulsants, and antipsychotics, which are associated with dangerous side effects, drug interactions, or low efficacy. Because of these drawbacks, opioids still retain a prominent role in pain management. While the true cost of opioid abuse is difficult to assess, the American Addiction Centers calculated \$2.5 trillion from 2015 – 2018 in the US¹. In addition, chronic pain costs the US \$ 635 billion a year, despite current treatments².

B. Description of your solution/novel approach

Somatostatin alleviates pain in humans^{3,4}, and while activation of either somatostatin receptors (SSTs) 1-4 can facilitate this, SST1, 2, and -5 produce endocrine effects, and SST1 is expected to produce growth hormone-, prolactin- and calcitonin-related side effects^{5,6}. The SST4 is expressed in the trigeminal ganglion (TG) and dorsal root ganglion (DRG), two major relays of pain and nociceptive information to the CNS but is otherwise mainly found in the brain^{7,8}. Hence, SST4 has been gaining



increasing attention for avoiding the known on-target side effects associated with the other SSTs. An SST1 and -4 selective peptide (TT-232), originally investigated for cancer treatment, was subsequently shown to alleviate pain, and more recently, the same was shown for small molecule SST4 agonists^{3,4}. Our approach relies on cone snail toxins, exploiting the millions of years of evolution that has produced drug-like molecules, and an FDA approved drug (Prialt). This resulted in the discovery of the compound HSH-109, as well as improved analogs, comprising the first series of truly SST4-selective peptides.

C. Uniqueness of your solution/difference to the current 'Gold Standard'

The most widely used drugs for any pain indication are opioids. In 2009, the seven major markets (7MM) saw more than one third of pain medication sales value coming from opioids, with another third from non-steroid anti-inflammatory drugs (NSAIDs), and anticonvulsants and antidepressants taking up 13 % and 11 %, respectively⁹. While opioids are certainly effective for some pain indications, they are highly addictive and 20-30% of patients receiving long-term opioid treatment developing an opioid use disorder¹⁰. However, opioids are often used for pain indications despite showing minuscule effects¹¹, and the same is true for anticonvulsants which are even used in cases with no reliable evidence of positive effects but a high degree of known adverse effects^{12,13}. NSAIDs are often not well suited for severe pain, and are associated with side effects, including gastrointestinal complications, cardiovascular events, renal toxicity, and hypertension¹⁴. Due to the expression pattern of SST4, we believe that our approach is associated with far fewer and less severe side effects⁸. Further, previous studies with somatostatin or SST agonists in human patients, as well as SST4 agonists in animal pain models suggest that our approach will be suitable for treating several of the pain indications that are most problematic in the current clinical setting, including chronic lower back pain¹⁵, inflammatory pain¹⁶, cancer pain¹⁷, as well as post-surgical pain and neuropathic pain¹⁸ (see also Fig. 1 in Part 2).

D. Your suggested main market, and/or other market areas and niches

With 187 million people in the 7 major markets (7MM) suffering from various chronic pain indications, and due to the lack of good alternatives, opioids are still widely used. Based on our in vivo data and the mechanism of action, our compound is expected to be effective at treating lower back pain, musculoskeletal pain disorders, osteoarthritis, and neuropathic pain disorders that had a combined 7MM market value of more than \$ 17 billion in 2020 (see previous section). The global market for opioids was more than a 25 billion in 2018, and we aim to largely replace opioids, but also provide an alternative for pain indications where not even opioids are sufficient, e.g., neuropathic pain. However, we will initially focus on the neuropathic pain market.

E. Competitors

Competitors should be divided into the current market (described above) and the pipeline, of which ~40 % targets neurotransmission, ~20 % targets ion channels, ~10 % targets prostaglandin signaling¹⁹. In neurotransmission, a surprising 40 % focus on opioids. A significant portion of the remaining neurotransmission pipeline relates to the endocannabinoid system which is concerning due to the broad expression pattern of receptors (CB₁ and CB₂), and particularly the known effects of cannabinoid receptor activation on heart rate and blood pressure due to myocardial expression²⁰. The ion channel modulators are divided between numerous specific targets, though a large portion target Na⁺ channels (~45 %) or Ca²⁺ channels (~20 %). Current Na⁺/Ca²⁺ targeting drugs and drug candidates are typically

G. What part of your technology is or can be patented?

Composition of matter priority patent application has been filed on the peptide and any relevant analogs. During the next months, I will test additional analogs to broaden the claims.

H. Applicant credentials

I have a background in molecular pharmacology and cone snail toxin research and have years of experience in both early drug development and analog optimization, as well as experience working with the specific type of compounds we have identified. I am strengthening my business development skills, participating in the “Entrepreneurship in Healthcare” course at BI Oslo with an accompanying mentor to assist in business plan development. I expect to be able to lay out our initial business plan after this course and have a good overall understanding of the business development aspects of a future spin-out. However, in the long term, we will recruit a dedicated business development partner.

I. Feasibility

All the *in vitro* GPCR testing is routinely performed in house, and the pain models are routinely performed by our collaborator. We have obtained quotes for and expected timeframes for the CRO activities (Task 1.2, and 2.2), and they are well within feasibility.

J. Risk assessment

The major risks during the SPARK timeframe is listed here. In parenthesis is the estimated likelihood on a 1 – 5 scale (1 is low, 5 is high):

- Not securing sufficient funding (3).
- Compounds activating opioid receptors (1).
- Compound interfering with P450 enzymes (1).
- Compounds eliciting addictive- or reward phenotypes in animals (2).
- Compounds eliciting significant toxic- or side-effects (2).

The majority of these risks will be mitigated by having a range of analogs, and further developing the compound(s) should any of these problems arise. Further, there are some minor risks that will not derail the project entirely but would change certain parameters of how we proceed. These include:

- Compound not crossing intestines (not orally active) (3).
- Compound displaying high plasma protein binding (3-4). *
- Compound having low solubility (mainly an issue if it is not orally active and needs to be formulated for injection solutions. Optimizations can then be performed) (2-3).

** This might be beneficial, as this could decrease the dosing frequency if exploited effectively.*

These will be overcome in the same way as the risks described above.

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Part 2: Attachments

SPARK Denmark

Project title:	Non-opioid pain relief through a novel target
Applicant:	Walden Emil Bjørn-Yoshimoto

Content

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A. Motivational letter

My plan is to create a spinout (tentatively in 2024). To do this, I am very interested in the industry mentor, as the industry and business aspects of this is something I have only very limited experience with.

Although I have, prior to my PhD, worked in a small company (a spin-out from the University of Copenhagen, though I joined after their true “start-up” phase), I still have quite limited experience with every aspect of this venture that is not strictly related to the science and research. While I am doing what I can to prepare (taking courses in Healthcare Entrepreneurship, reaching out to contacts who have, and are currently starting companies, etc.), I am very interested in the industry mentorship, and see this as an immense asset for a researcher starting a commercial venture.

While the funding associated was not the main driver for my application, this is also a very welcome boost to the feasibility of eventually creating the spin-out. As it stands, we cannot use any significant amount of funding from academic project to further the commercialization efforts outside of what will also be used for academic articles we will publish on the subject. While we are very excited about the IP, and believe this holds great potential, we are experiencing that some funding agencies find the project is in “too early a phase” to apply for their funding. As such, the funding associated with the SPARK program can help drive the project to a stage where we will be considered for some initial (soft) funding for the next stage, and thus the SPARK-associated funding may prove pivotal in the feasibility of eventually commercializing the asset and creating a spin-out.

B. Preliminary/proof of principle data

We discovered the first somatostatin agonist cone snail toxins (called ‘conotoxins’) earlier this year¹. The initial conotoxin, Ro1, was an agonist at the somatostatin receptors (SST) 1 and 4, showed pain relief in two mouse models and was very stable in plasma. Interestingly, Ro1 did not elicit a response when screened at the opioid receptors, and elicited pain relief only when injected intraperitoneally, not when injected intrathecally (in the CNS). The discovery of Ro1 enabled us to identify numerous others consomatins, among those were one (HSH-109) that showed an increased potency and selectivity at the SST4 compared to Ro1. HSH-109 was tested in two mouse models of pain, a post-surgical pain (paw incision) model and a model of neuropathic pain (the spared nerve injury, SNI):

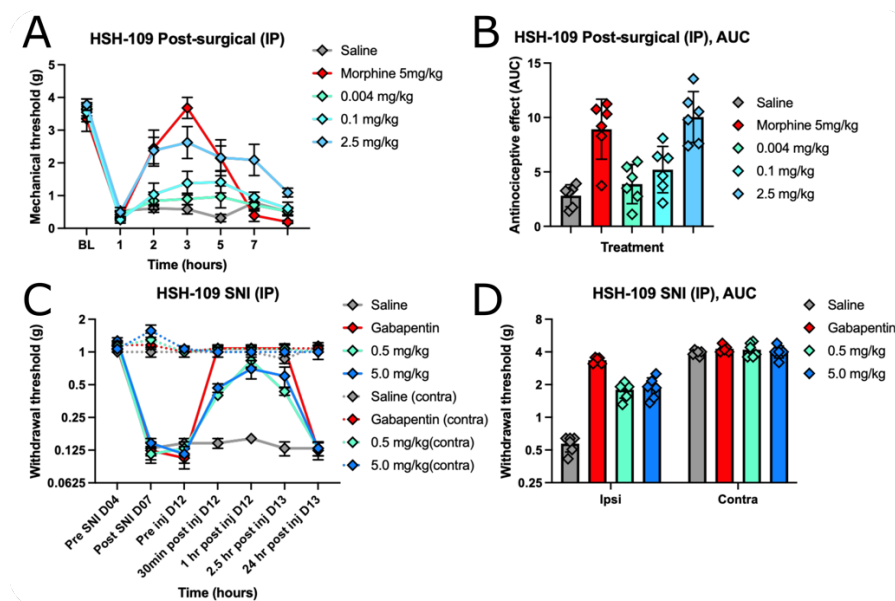


Figure 1 – Effect of HSH-109 in mouse pain models. A-B, the post-surgical pain model. A, the effect over time. B, the area under the curve from the left graph. C-D SNI model. C, the effect over time. The full lines represent the ipsilateral side (ipsi, the injured side), while the dashed lines represent the contralateral side (contra, the uninjured control side). D, the area under the curve from the left graph.

Subsequently, we have developed numerous analogs, several with improved potency and selectivity at the SSTs:

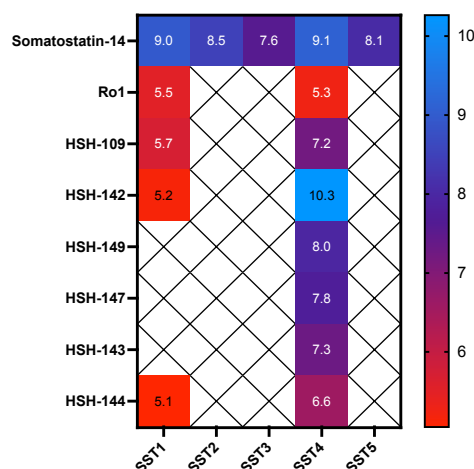


Figure 2 – Heatmap of pEC_{50} value for Somatostatin-14, Ro1, HSH-109, and select HSH-109 analogs. A white background with an “X” indicates that the concentration-response curves did not complete when using a maximum concentration of 300 μ M, thus a reliable EC_{50} value could not be obtained. However, this means that the C_{50} value would certainly be higher than 10 μ M ($pEC_{50} < 5$).

References:

- 1 Ramiro, I. B. L. et al. 2022. *Science Advances* **8**, eabk1410 (2022).
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C. Anticipated budget

See below

D. CV

See below

SPARK Denmark Budget		SPARK DENMARK	
Applicant:	Walden Bjørn-Yoshimoto		
Team members:	Walden Bjørn-Yoshimoto	Helena Safavi	Sara Hestehave
Title of project:	Non-opioid pain relief through a novel target		
Institution:	University of Copenhagen		
Department:	Department of Biomedical Sciences		
Laboratory name and address:	Safavi-Lab, Nørre Alle 14, 07-9-56, 2200 København N		
Legal signatory, Head of Department/Center (name & title):	Head of Department, Cathrine Ørskov		
Date and signature ¹ :	07-10-2022		

¹ By signing you certify that your department/center/company is aware of the requirements and economic risks associated with the SPARK program.

Budget must be in DKK ²	Financed by SPARK Denmark	Co-financed by xx	Co-financed by xx	Co-financed by xx
Year 1	Max. DKK 350.000 per year.			
Salaries SPARK Denmark will not cover salary for main applicant (PI) and co-applicants. Applicants may apply for funding for salary for research assistance, employees or project consultants at all staffing levels, including project management (including technical and administrative assistance).				
Consumables for peptide analog testing and opioid receptor testing	50,000			
Test physiochemical, Caco-2, initial stability of select analogs (CRO, Bienta)	200,000			
Animals for finding dose-range + testing additional analog in vivo	100,000			
Annuum				
Running costs				
Apparatus				
Support staff (technical-administrative)				
Subtotal				
Year 2	Max. DKK 350.000 per year.			
Salaries SPARK Denmark will not cover salary for main applicant (PI) and co-applicants. Applicants may apply for funding for salary for research assistance, employees or project consultants at all staffing levels, including project management (including technical and administrative assistance).				
Connditioned place preference test (WuXi AppTec)	300,000			
Animals for CFA model	50,000			
Annuum				
Running costs				
Apparatus				
Support staff (technical-administrative)				
Subtotal				
Total	700,000	0	0	0

Curriculum Vitae

Name: Walden Emil Bjørn-Yoshimoto

Date of birth: June 27th 1983

Place of birth: Honolulu, HI, USA

Citizenship: Dual – Danish and US

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Work experience and education:

- 2022 – **Assistant Professor** at the University of Copenhagen, Department Biomedical Sciences.
- 2020 – **Freelance Consultant** and Founder of Walden Consulting.
- 2019 – 2022 **Postdoc** at the University of Copenhagen, Departments of Biology and Biomedical Sciences.
- 2017 – 2018 **Postdoc** at the University of Copenhagen, Department of Drug Design and Pharmacology.
- 2013 – 2017 **PhD Student** at the University of Copenhagen, Department of Drug Design and Pharmacology.
- 2016 – 2017 **Research assistant** at the University of Copenhagen, Department of Drug Design and Pharmacology.
- 2011 – 2013 **Research scientist** (2012-2013) and **research assistant** (2011) at Evolva S/A
- 2004 – 2010 **BSc and MSc in Biochemistry** from the University of Copenhagen.

Scientific output:

- Articles 16 Peer reviewed, 1 as corresponding author. ORCID: [0000-0003-1019-9239](https://orcid.org/0000-0003-1019-9239).
- Patents 1 patent awarded, 1 pending (priority patent filed).
- Reviewer Since 2021 I have routinely reviewed articles for several journals, incl. Basic & Clinical Pharmacology & Toxicology, Marine Drugs, Toxins.
- Outreach I have participated in various outreach activities and programs, including by giving presentations for schools from 2. grade through “3. g” at gymnasium, presentations and workshops for “Kulturnatten” (Copenhagen Culture Night), as well as writing popular science articles for “videnskab.dk”.

Scientific visits:

- 2015: Laboratory of Molecular and Cellular Neurobiology in the Section on Molecular and Cellular Signaling at NIMH/NIH, Bethesda, MD, USA. This is the laboratory of Dr. Susan Amara.
- 2014: ICCB-Longwood (Harvard Medical School) / Boston Children’s Hospital, Harvard Medical School, Boston, MA, USA. This was done primarily in the laboratory of Professor Clifford Woolf.

Teaching Experience:

Since 2016 I have supervised 3 students and 2 postdocs. Officially one pharmacy student and one PhD student, and unofficially, one PhD student and two postdocs.

Since 2013 I have taught various courses both lectures, classroom teaching, and lab exercises, to pharmacy-medicine-, and odontology students. They have ranged from bachelors’ courses to PhD courses and have included four different pharmacology courses, one medicinal chemistry course, and one biochemistry course.

Voluntary study-related work:

- 2009-2010: Member of the initiative group for LINK, alumni-association for biochemistry and molecular biomedicine at the University of Copenhagen.
- 2007-2008: Elected student spokesman for Biochemistry at The University of Copenhagen, where I worked closely with the head of studies for biochemistry.
- 2006-2009: Founding board member of the student café and social events house for the hard sciences (mBAR).
- 2006-2006: Elected member of the staff-student committee for Biochemistry at the University of Copenhagen.
- 2005-2009: Member of the student body for Biochemistry at the University of Copenhagen.

Grants Awarded:

- 2015: Augustinus Foundation DKK 20,000 travel award for a research stay in Dr. Susan Amara's lab at NIMH/NIH, Bethesda, MD, USA.
- 2015: International Society for Neurochemistry (ISN) USD 2,450 travel award to attend the ISN conference in Cairns, QLD, Australia.

Publications and Patents:

Asterisk (*) indicates first authorship for Bjørn-Yoshimoto, W.E.

Copyright symbol (©) indicates corresponding/senior authorship for Bjørn-Yoshimoto, W.E.

16 peer-reviewed articles, 1 patent granted. **H-index: 9.** ORCID: [0000-0003-1019-9239](https://orcid.org/0000-0003-1019-9239).

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