HBC Discovery Science Delivering New Drug Leads

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Author:
Dr. Crawford Currie, Head of Medical R&D

New potential pharmaceutical drug leads by HBC

Introduction

As noted in the CEO Statement in our Q3 Financial Report issued today, 5 November 2021, Hofseth BioCare ASA ("HBC") is a consumer and pet health ingredient supplier and an incubator for new drug leads. Our ability to delineate the unique health benefits of our ingredients has resulted in both unique health claims as well as patent filings to protect the underlying IP. However, this work has also led to the discovery of a number of potential pharmaceutical drug leads.

Led by our CSO, Bomi Framroze, this discovery work has identified (1) a unique lipopeptide compound in OmeGo® that targets type 2 / allergic inflammation, (2) a set of structurally related peptides that help the body correct iron deficiency anemia and (3) a peptide group that reduces GI inflammation and enhances GI barrier function. All our GI discovery drug lead work is in collaboration with a world leading research centre, Stanford School of Medicine.

HBC continues work to optimise the bioactivity of these potential therapeutic agents and maximise IP protection. Once we have fully elucidated the bioactivity of the drug leads, priority disease targets will be defined. This work will also factor in conditions where approved oral treatment options are either limited or not available. Strategic options will also be determined as how best to proceed with clinical development and optimise value to HBC shareholders.

Synthesis of a potential oral therapeutic, targeting eosinophilic diseases

Our efforts at developing an oral pharmaceutical lead program to treat inflammatory disease driven by eosinophils is on-going, with rapid success. We have made twenty-four SAR (Structure-Activity Relationship) analogs, derived from the unique lipopeptide contained in OmeGo. One of these, MA-022, has shown a marked and clinically significant level of eosinophil control in eosinophils derived from humans with allergy. Measures of eosinophil control included eosinophil apoptosis (programmed cell death) and CD11b integrin expression (which eosinophils use to attach to the site of inflammation/ irritation).

A background to eosinophilic diseases

The inappropriate activation of eosinophils is a well-recognised driver of a number of inflammatory diseases including asthma, chronic rhinitis, and various gastrointestinal diseases, including eosinophilic oesophagitis. Steroids, both topical and systemic, remain a cornerstone of treatment and can be highly effective. However, some individuals suffer side effects, an inadequate response to treatment, or both.

Stage 1: Profiling our lipopeptide

To date we have assessed the efficacy of the lipopeptide in OmeGo®, our enzymatically liberated fish oil, in two animal models of eosinophilic inflammation. These studies have been submitted for publication and show a consistent inhibition on eosinophil function on all pre-defined measures. The studies contained both positive and negative controls to help better define the anti-eosinophilic activity especially versus agents with well-defined anti-eosinophilic activity. The enhanced anti-eosinophilic activity of the MA-022 compared to the lipopeptide contained in OmeGo® gives us significant confidence that MA-022 has the potential to be an oral therapy targeting eosinophilic inflammation.

In the HDM study the lipopeptide showed a similar level of eosinophilic inhibition compared to the CRTH2 antagonist fevipiprant. Note that whilst fevipiprant failed to get over the line at phase 3 in asthma the analog has a markedly greater anti-eosinophilic effect than the lipopeptide. We also know that once we reach a threshold of anti-eosinophilic activity a therapeutic benefit is seen in asthma as per the anti-IL-5 biologic therapies.

In the guinea pig study, the lipopeptide showed a similar but numerically greater inhibition of eosinophils compared to apolipoprotein A-IV (APOA-IV). APOA-IV is an endogenous protein that has broad anti-inflammatory effects including anti-eosinophilic actions. In asthma the levels of APOA-IV are reduced.

Stage 2: protecting our IP; patent filings for the analogs & lipopeptide

Together with the other analogs we have produced, MA-022 is the subject of a new US/PCT patent filling, filed in June 2021. After the patenting process is complete, we will apply for New Chemical Entity (NCE) status in the US. This will further enhance the patent protection including patent duration.

Patent protection for the lipopeptide is also ongoing and the publication of our patent application was published on 14 Oc-

tober 2021. Key elements contained in the patent application are: detailing the in-vitro and preclinical work demonstrating the anti-eosinophilic action of the lipopeptide, patent claims around reducing eosinophil effector function by a salmonid oil obtained from mild enzymatic hydrolysis off-cuts of salmonid fish, a method for treating eosinophilic inflammatory conditions and diseases in human by salmonid oil derived from our enzymatic process with conditions listed including asthma, viral respiratory disease severe acute respiratory syndrome administered either orally (by multiple formats such as a syrup capsule or soft gel), by inhalation, by injection or topically.

For more details on the patent application please use the following link: https://bit.ly/3wjUqgU

Stage 3: scaling the synthesis of the analogs

Our priority now is the scaling up the synthesis of MA-022 followed by the initiation of studies in relevant animal models of eosinophilic inflammation. Once the preclinical work is completed, based on the overall profile of the analog we will be well placed to decide the diseases and patient segments that should be prioritised for clinical development.

Two potentially addressable markets: asthma and GI eosinophilia

Asthma is a common condition, affecting an estimated 7-8% of the population with 90% of patients suffering mild to moderate asthma. Inhaled and oral steroids remain a cornerstone in the management of asthma. They are often effective at improving lung function and reducing asthma exacerbations. However, with long term use there is the concern over the potential for side effects, including cataracts, osteoporosis and diabetes. Furthermore, inhaled therapies require healthcare professionals to train the patient in how to use the device effectively and even so many patients have suboptimal technique thereby limiting the dose of steroid reaching the lungs. An oral treatment option would enhance convenience for both patients and healthcare professionals and help reduce steroid daily dosing requirements, a highly attractive proposition. The branded market for steroid-containing inhalers for asthma and COPD currently have sales of over $6bn despite significant generic alternatives which have restrained the branded inhaler prices. We are not aware of any oral anti-eosinophilic agents in development for the treatment of asthma.

Eosinophilic inflammation can affect a number of sites in the GI tract including the oesophagus and the stomach. These result in chronic symptoms including pain, difficulty in swallowing and bloating. Overtime, the inflammation in the gut wall can result in fibrosis worsening symptoms and making them harder to treat. There are an estimated 320,000 patients with eosinophilic oesophagitis in the US and EU5 combined and around 50,000 with eosinophilic gastritis. However, it's felt that these numbers under-estimate the true incidence and as better treatments emerge diagnosis rates will increase.

No agents are currently approved for any forms of GI eosinophilia. The mainstay of treatment remains topical steroids (swallowed to coat the lining of the gut) and elimination diets. Several injectable biologics therapies are in clinical trials for GI eosinophilia which are already licensed for the treatment of severe asthma and retail at an annual cost of $15,000-$20,000. We know of no novel, targeted therapies in development for GI eosinophilia. The only development work appears to be re-formulated steroids and antihistamines.

Treatment of iron deficiency anemia (IDA): peptide identification

Iron deficiency anemia (IDA) is the commonest blood disorder globally and in part reflects the difficulty the body has in extracting iron from the gut as well as nutritional inadequacy. Women of childbearing age are most commonly affected by IDA and this can have a deleterious effect on fertility both in terms of conceiving as well as reducing the likelihood of a successful pregnancy. Beyond fertility, IDA can cause numerous symptoms including fatigue, reduction in exercise capacity, shortness of breath on exertion and headaches.

Currently dietary modification or iron supplementation, either via tablets or injection, are the way most people address a need to increase body iron stores to improve hemoglobin blood levels and either treat or prevent anemia. However, dietary modification is often impractical for social, economic or cultural reasons. In contrast, whilst iron supplementation is broadly accepted it frequently causes gastrointestinal side effects including nausea, constipation and bloating limiting compliance and hence its utility. Importantly, iron supplementation also carries the risk of toxic effects on the body from iron overload.

As previously announced, ProGo (16g daily) has been granted unique structure-function claims by Health Canada including the maintenance of healthy ferritin and hemoglobin levels even though it contains no iron. The approval represents the demonstration of the bioactivity of the peptides in raising FTH1, the gene encoding the heavy chain of ferritin. The body uses ferritin to store iron safely and to release it in a controlled manner to where it is needed.

Having already identified the peptides driving the FTH1 effect the peptide lead structure novelty searching is on-going. This work has already shown that some of our active peptides are previously unknown and hence novel structures. This will enable filing for novel composition of matter status with the associated durable IP protections.

We have completed an in silico study to expand the scope of active structures from our core 6-mer bioactive peptide lead.

This should lead to a broader IP claim set, improved anemia-reducing bioactivity and broaden the scope for our ongoing process development work. Ultimately this will enable us to increase the concentration of these peptides in our salmon protein hydrolysate and result in an IDA-SPH capsule during 2022 to target the treatment of anaemia.

Bioactive peptides targeting Gastro-Intestinal (GI) Inflammation

Inflammatory bowel disease is a chronic condition that can affect both physical health and quality of life (QoL). The inflammation means that the lining of the gut is a less effective barrier both from reduced mucus secretion and disruption of the junctions between the cells that comprise the gut lining. This can then result in gut bacteria crossing the lining and driving an immune response with further inflammation.

Symptoms include crampy abdominal pain, diarrhoea and weight loss. Ongoing blood loss from the bowel can result in anaemia further exacerbating the impact on QoL with anaemia symptoms including fatigue and reduced exercise capacity. Long term effects of bowel inflammation include an increased risk of colon cancer. There are more than 70,000 new cases of IBD diagnosed each year in the US alone. Steroids and biologic therapies are commonly used treatments. Whilst these can provide significant benefit and are generally well tolerated, they are associated with side effects such as osteoporosis and diabetes with long term steroid use and serious infection with biologic therapy. Furthermore, a significant number of patients do not attain full remission and continue to suffer from the effects of IBD. There is therefore a clear need for further, well tolerated treatments which can help to attain and maintain remission for these patients.

Stanford School of Medicine collaboration: pre-clinical work to date

We have successfully completed the first in-vivo study demonstrating the prophylactic effect of SPH peptides on reducing intestinal injury. The study used a mouse model of inflammatory bowel disease (IBD) and is part of our multi-year research collaboration with Prof. Karl Sylvester at Stanford University School of Medicine. This pilot study demonstrated the effectiveness of SPH peptides to reduce TNBS-induced IBD (inflammation induced by trinitrobenzene sulfonic acid). The results showed that SPH at 1% concentration in drinking water provided substantial protection to the GI tract from TNBS-induced damage. This protective effect was demonstrated by all criteria pre-defined to assess gut health, namely i) colon length ii) fecal occult blood test (to assess for bleeding from the gut wall) and iii) Stanford's proprietary fecal K8 assay (a marker of damage to the lining of the gut). It is note-worthy that the 1% concentration in this assay is equivalent to an adult human dose of 10g/day.

We are now carrying out a larger preclinical TNBS induced colitis mouse assay, powered for statistical significance with the SPH peptides compared to a negative control peptide. This will control for any nutritional effect. Blood serum and tissue MOA (mode of action) analyses at optimum SPH bioactive peptide dosing, will move us further towards the development of our Necrotizing Enterocolitis (NEC) and Inflammatory Bowel Syndrome indications. This work further builds on our prior research which has shown a 4-5 fold increase in the expression in the HO-1 gene which increases heme-oxygenase activity which helps to reduce gut inflammation and improve gut epithelial (lining) barrier function.

Early-stage discovery programs

With >500 bioactive peptides contained within SPH, we have a number of early-stage programs ongoing to identify and profile the properties of the different peptide groups. The core of our identification work revolves around gene and protein expression work. This has directed us towards researching the bioactivity of the peptides in a number of conditions including, acne, a very widespread and troublesome inflammatory skin condition that often leads to scarring of the face and psychological distress.

Acne — highly encouraging early data

Acne begins at puberty and is the result of several factors including blockage of the sebaceous gland follicles producing discrete swellings as well as subsequent increasing bacterial numbers in the follicles resulting in inflammation and infection and the discharge of pus. Treatments include the topical application of benzoyl peroxide as an anti-bacterial, antibiotic tetracycline preparations as well as steroids to reduce inflammation. However, these treatments are not universally successful in resolving acne and do come with side effects, in particular prolonged topical steroid use and the risk of thinning of the skin.

Our Discovery Research programs on acne treatment with bioactive peptides was completed this quarter and an extensive report with multiple invitro assay results was issue. Our initial results indicate that cationic peptides within our SPH could help in both reducing inflammation and C. acnes colonization. Hence these cationic peptides could lead to an important co-treatment alongside currently used anti-acne therapy to reduce their significant side-effects and extend their therapeutic potential.

Other areas of interest with positive signals

Finally, our research in a) islet cell protection to retard the progression of pre-diabetes to type II diabetes, b) prostate cancer co-treatment using fractionated peptides in SPH, and c) chronic fatigue syndrome continue to progress with encouraging results being followed-up.

Accelerating our discovery research with external collaborations

Whilst we have previously focused our discovery research at our lab at Menlo Park the discovery of many more potential treatment leads means we need enhanced capacity to further explore these at the discovery phase, in a timely manner. We are therefore collaborating with both NOFIMA and Marbio to these ends. This research program has fractionated the SPH peptides by molecular size and by polarity. Several further anti-inflammatory actions have been discovered. Of particular note is the significant reduction of Nf-λB activity as well as a significant reduction in several inflammatory cytokines. This includes a 40-46% reduction of TNF-α production in two different human cell lines. These hold an exciting potential in both the treatment and prevention of diseases associated with excess inflammation. This work has been pursued further with NOFIMA and Marbio in Q3 2021, and we expect to publish the findings in Q4 2021.

This is Hofseth BioCare

HBC is a Norwegian biotech company that develops high-value ingredients and finished products. The ingredients are in various stages of discovery and preclinical development in collaboration with multiple clinics and university research labs in several countries.

HBC is a Norwegian consumer and pet health ingredient supplier and an incubator for new drug leads. Research is ongoing to identify the individual elements within its ingredients that modulate inflammation and the immune response with pre-clinical studies in multiple clinics and university research labs in several countries. Lead clinical and pre-clinical candidates are focused on developing an oral pharmaceutical lead program to treat inflammatory disease driven by eosinophils. Preclinical trial work with the oil is ongoing to ameliorate lung inflammation in eosinophilic asthma and COPD ("smokers lung") as well as clinical work in COVID. Other leads are focused on the protection of the Gastro-Intestinal (GI) system against inflammation (including ulcerative colitis and the orphan condition necrotising enterocolitis) and using peptide fractions of salmon protein hydrolysate (SPH also known as 'ProGo') as a Medical Food to help treat age-related Sarcopenia, and as a treatment for Iron Deficiency Anemia.

The company is founded on the core values of sustainability, optimal utilization of natural resources and full traceability. Through an innovative hydrolysis technology, HBC can preserve the quality of lipids, proteins and calcium from fresh salmon off-cuts.

HBC's headquarters are in Ålesund, Norway with branches in Oslo, London, Zürich, Chicago, Palo Alto and Tokyo.

HBC is listed on the Oslo Stock Exchange with ticker "HBC".

OUR PRODUCTS AND INGREDIENTS

Ingredient	About	Finished products
Sustainable. Pure. Proven. OmeGo® Full Spectrum Omegas	Fresh unrefined salmon oil. Produced with 4 years shelf life, full spectrum of omegas and natural antioxidants.	Cardio Salmon Oil™ for human consumption and Brilliant Salmon Oil™ for pets
Sustainable. Pure. Proven. ProGo® Bioactive Peptides	Salmon protein hydrolysate. Peptides for fast uptake, and documented BMI reduction, hemoglobin and energy increase.	Endurance Protein™ series as sports nutrition for athletes, active and people looking for a high quality, hypoallergenic protein source
Sustainable. Pure. Proven. CalGo® Calcium Collagen Complex	Marine bone powder, as hydroxyapatite form of calcium for best bone growth and density increase.	Strength Calcium™ as tablets for human consumption

IR CONTACTS

James Berger, Chief Commercial Officer
Tel: +41 79 950 1034
E-mail: jb@hofsethbiocare.no

Jon Olav Ødegård, Chief Financial Officer
Tel: +47 936 32 966
E-mail: joo@hofsethbiocare.no

Dr. Crawford Currie, Head of Medical R&D
Tel: +44 7968 195 497
E-mail: cc@hofsethbiocare.no

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