Foxy-5
A unique Phase 1 opportunity to combat the spreading of cancer

Wnt RESEARCH

Why WntResearch is developing novel anti-cancer drugs

- **Approximately 55 000 Swedish citizens are diagnosed with cancer every year** *(Cancerfonden 2012).*

- **Approximately 23 000 Swedish citizens die every year from cancer** *(Cancerfonden 2012)***.**

Agenda

- Company and background
- What is cancer?
- What is *Foxy-5?*
- Phase 1/1b studies
- Phase 2 study
- *Box-5*
- Questions

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WntResearch summary

- **Founded in 2007 and listed on AktieTorget in 2010 (ticker: WNT)**
- **Focused on cancer therapy**
  - Proprietary products and technology to combat cancer metastasis (spreading)
  - Phase 1 Clinical Trial initiated in 2013 (will finalize in spring 2015)
  - New exploratory phase 1b will be initiated in 2015
  - Unique profile with significant market potential
  - One of the first metastasis specific products to enter clinical development
- **Experienced and dedicated management team**
- **Lean and focused organization**
  - Virtual structure supported by Eurostars grant
- **Finance**
  - Raised equity: €8.4M
  - Eurostars grant and commitments from partners: €4.2M (3 + 1.2)

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WntResearch Management

Nils Brünner, CEO

- Professor, Faculty of Health and Medical Sciences, University of Copenhagen
- Published more than 350 scientific papers within cancer research with a focus on translational cancer research
- Has filed several patent applications and serves as medical advisor for a number of biotech companies.
- CEO WntResearch since 2012

Thomas Feldthus, CFO

- 20 years of industry experience within life science
- Co-founder of three biotech companies including Saniona and Symphogen
- Raised more than €200 million in venture capital
- Negotiated numerous collaboration and license agreements

Tommy Andersson
Co-founder and CSO

- Professor Experimental Pathology at the Medical Faculty, Lund University
- Published more than 100 peer-reviewed papers on intracellular signaling, cell adhesion and migration
- Inventor on the three patent families that form the basis for WntResearch

Ulla Hald Buhl
IR and Clinical Operation

- 17 years of Clinical Drug Development experience
- Director IR & Communications and Member of top Management
- Chief Clinical Operations and advisor in IR and Clinical Drug Development
- for biotech companies (two of them listed)
- Co-founder of two biotech Companies

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What is cancer and why is it so difficult to treat ?

A disease affecting the DNA in cells and with constant changes due to continous mutations

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Cancer Therapeutics

An Area with Significant Medical Needs and Market Potential

- **Cancer remains a disease with high unmet medical need**
  - Cancer affects one in three individuals and is the leading cause of death below the age of 75 in most Western countries. A 30-50% increase in cancer incidence is expected over the next 12-15 years
  - The overall mortality rates remain virtually constant despite enormous R&D efforts
- **Cancer combination therapies represent the way forward**
  - Combination of surgery, radiation, chemotherapy, targeted therapies and anti-angiogenesis therapies
- **Anti-metastatic therapies represent a huge medical need**
  - The primary tumor is rarely the cause of death of cancer patients
  - Mortality is the result of cancer cell spreading (metastasis) to other organs
  - Current therapeutics don’t target the metastatic process
  - Introduction of new anti-metastatic therapies in combination with existing therapies

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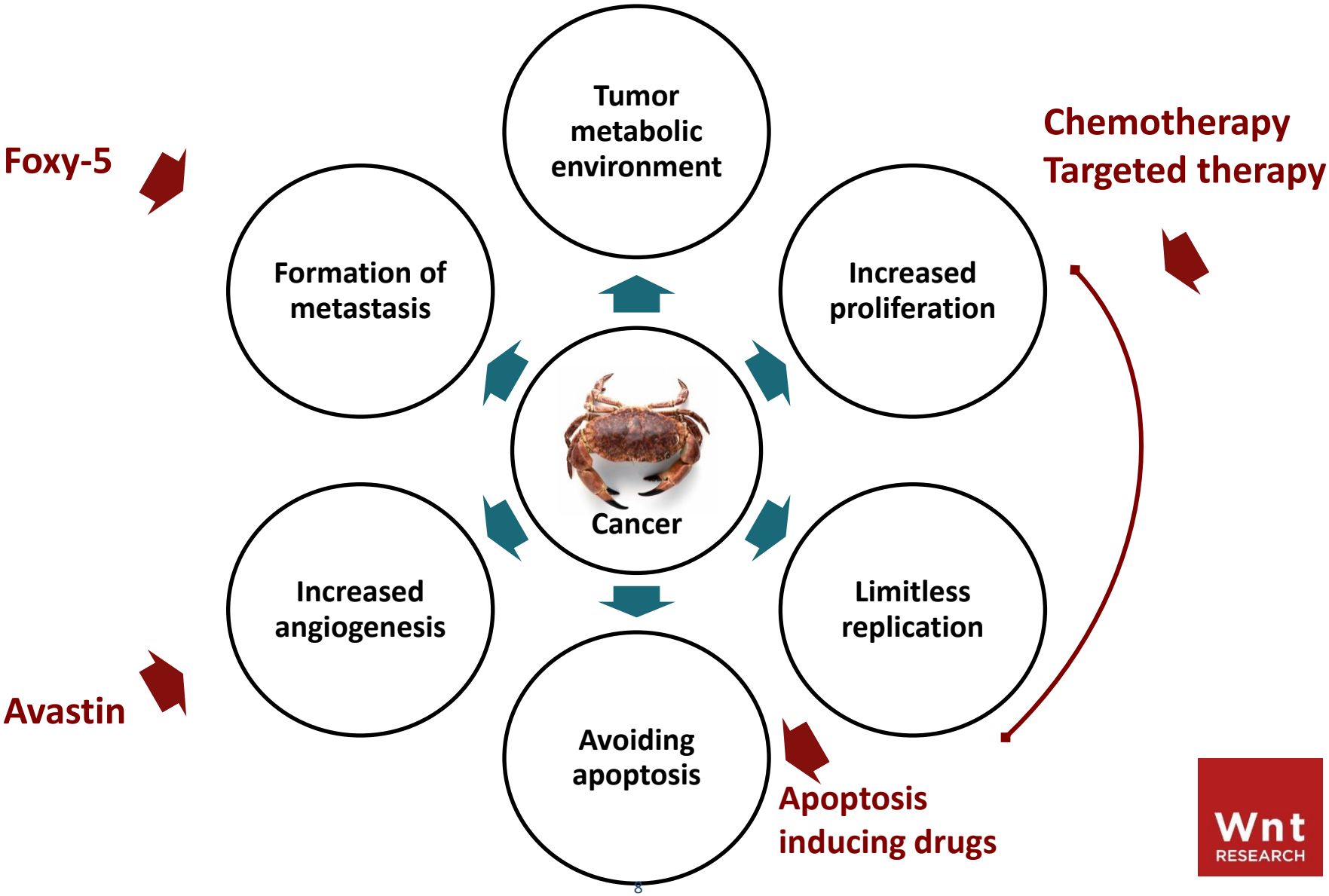
Tumor Formation Requires Several Changes in Cancer Cells

Existing therapies targets only a few of them



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Foxy-5
A Potential Blockbuster Product

Indication	Breast, colon and prostate cancer
Class	Peptide
MoA	Reconstitute the Wnt-5a signaling pathway of cancer cells thereby inhibiting cancer cell migration and their ability to form metastases
Objective	Develop a product with a unique and distinct MoA to be used in combination with other cancer therapies
Market	> $1 billion
Stage	Clinical trials
Launch	Potentially in 2019
IP Position	Patent protection at least until 2026 (USA 2028)
Next Key Event	Completion of Phase 1 spring 2015 Initiation of Phase 1b mid 2015 Initiation of Phase 2 late 2015/early 16

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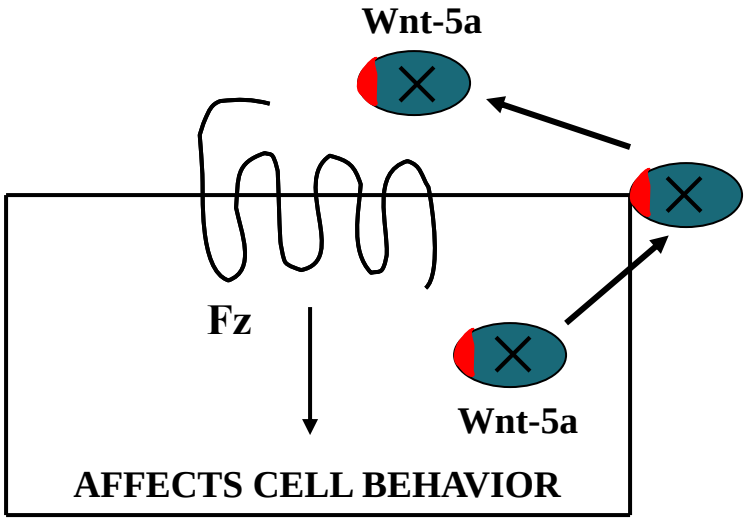
The Wnt-5a protein

- **43 kDa cystein rich glycosylated protein**
- **Role in development and cancer**
- **A secreted and extracellular protein**
- **Auto or paracrine signalling primarily via a 7TM Frizzled (Fz) receptor**
- **The auto and paracrine functions are aided by a heparan sulphate binding domain (red) whereby**
  - Wnt-5a binds to the membrane and is
  - effectively presented to the Fz receptor
  - following which it induces intracellular signalling



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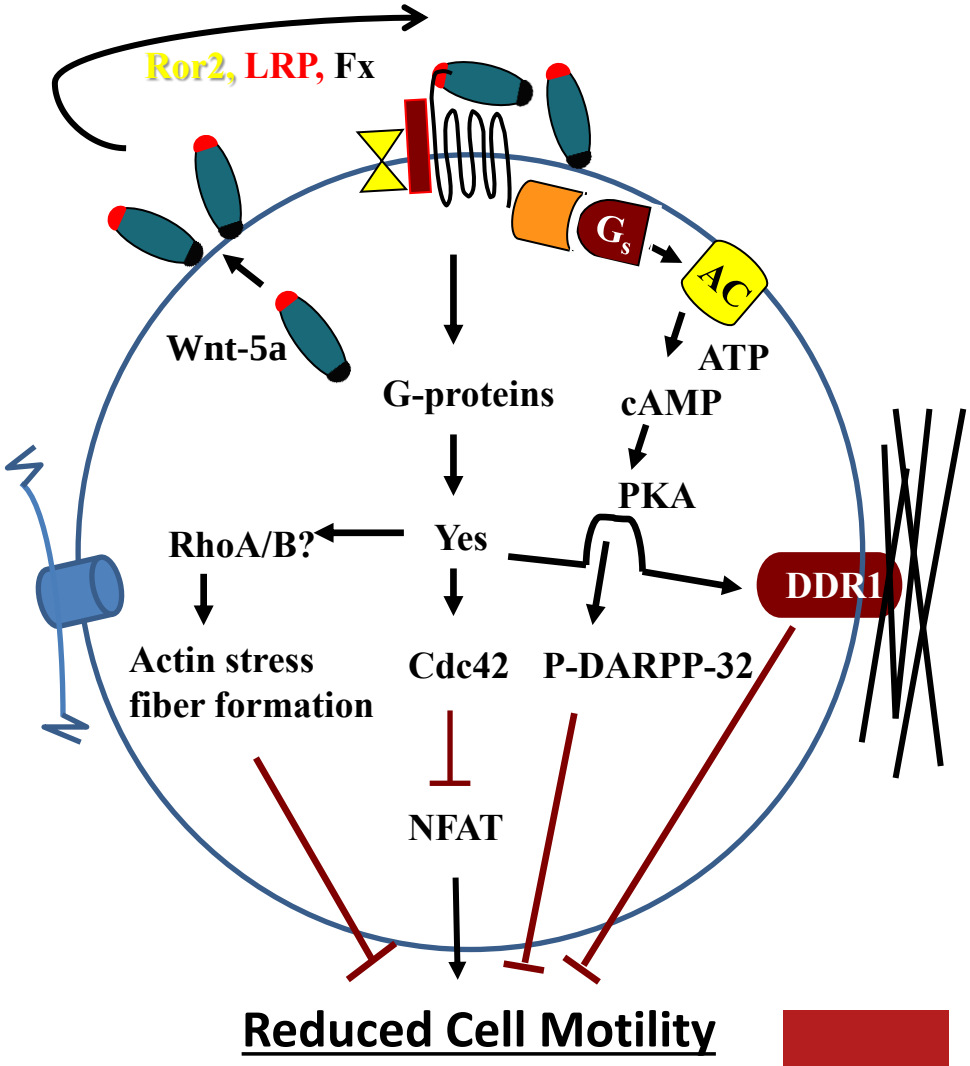
Mode of Action

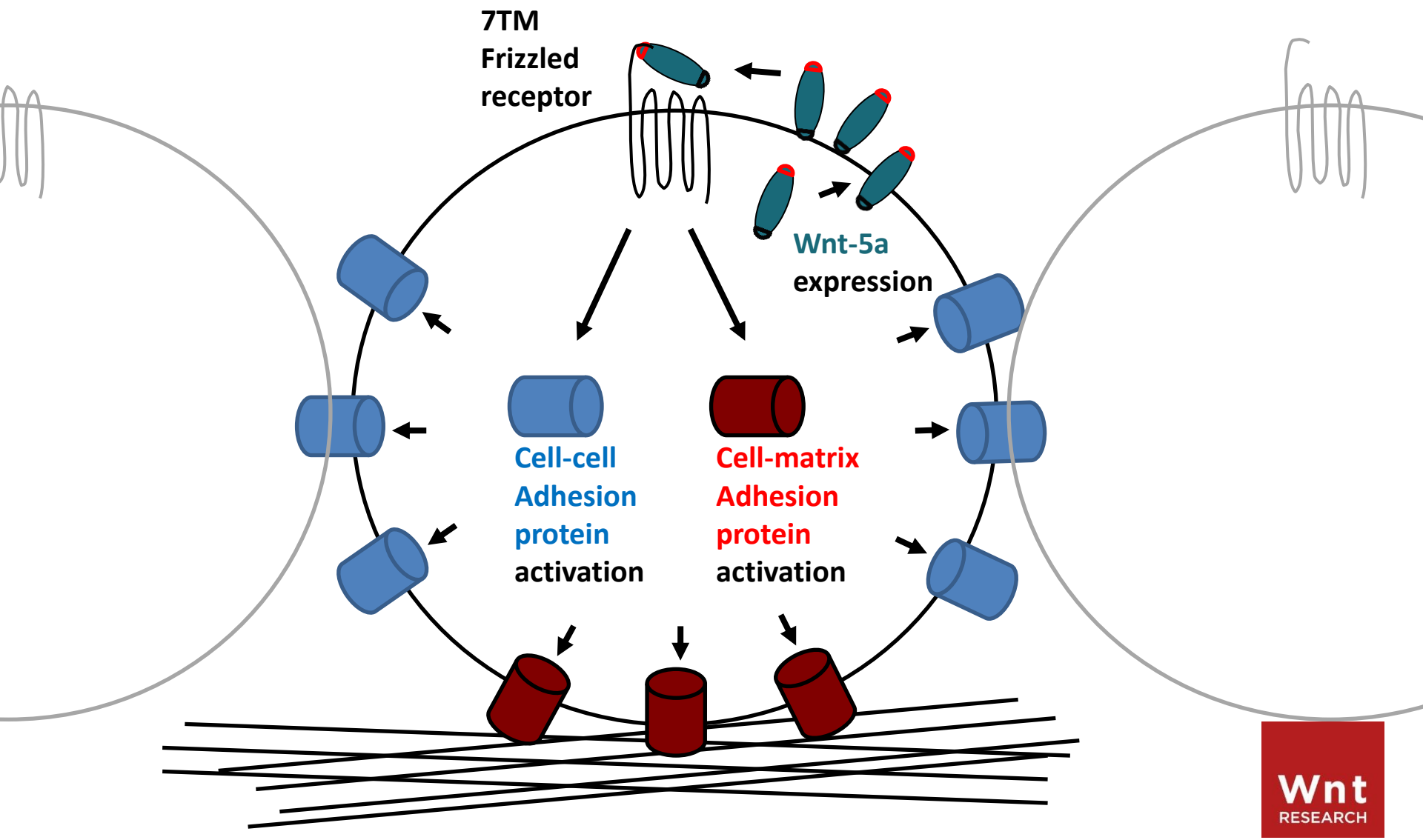
Wnt-5a and Foxy-5 transform cells to a immotile cell phenotype

- **Wnt-5a activates a number of pathways, which prevent cell motility**
  - activation of **cell-cell adhesion** proteins
  - activation of **cell-matrix adhesion** proteins
  - phosphorylation of DARPP-32 leading to **suppressed filopodia formation** and enhanced CREB activity
  - impairment of NFAT activity leading to **impaired migration**
  - reduction in ERK ½ signaling leading to **impaired migration**
- **Reconstitution of Wnt-5a signaling at cell surface initiates all the above mentioned events**



Mode of Actions

Wnt-5a Inhibits Cancer Cell Metastasis Formation



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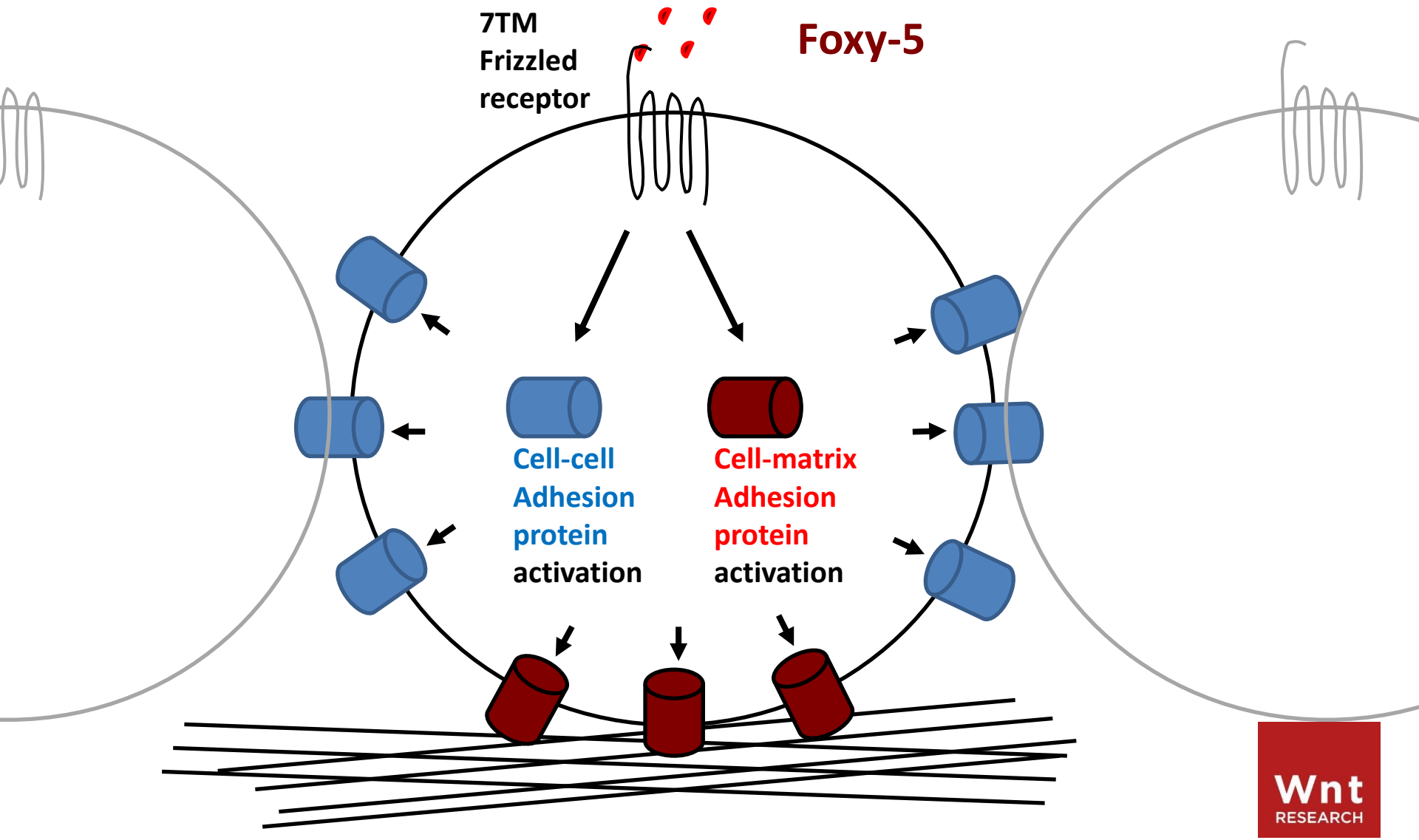
Mode of Actions

Foxy-5 Inhibits Cancer Cell Metastasis Formation



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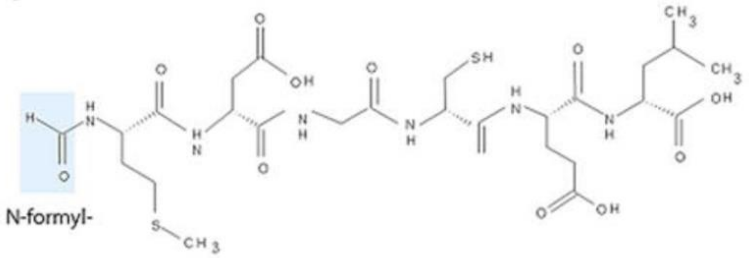
Foxy-5
A Hexa-peptide derived from Wnt-5a



- **rWnt-5a not suitable as a therapeutic agent**
  - Large protein (43 kDa)
  - Binds rapidly to heparan sulfate proteoglycans on the same or neighboring cells and is subsequently presented to frizzled receptors on respective cells
  - Heparan sulfate proteoglycans are linear polysaccharides, which are found in all animal tissue at the cell surfaces and extracellular matrix proteins

- **Foxy-5 peptide**
  - Comprises a Wnt-5 specific sequence of 6 amino acids plus a formyl group
  - Mimics the signaling and functional effects of Wnt-5a
  - Does not include the heparan sulfate proteoglycan binding domain
  - The N-formyl group protects against the digestion of the peptide

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Clinical evidence and preclinical research

- **Clinical studies**
  - **Wnt-5a protein expression -> good prognosis in breast cancer**
  - **Wnt-5a protein expression -> good prognosis in colon cancer**
  - Wnt-5a protein expression -> good prognosis in prostate cancer
  - No or low expression of Wnt-5a -> shorter recurrent-free survival due to increased metastasis
  - No or low expression of Wnt-5a -> reduced overall survival

- **Proof of principle studies**
  - Foxy-5 is a small molecule that mimics the effect of Wnt-5a
  - Foxy-5 and Wnt-5a binds to frizzled receptors
  - Foxy-5 and Wnt-5a inhibits breast, colon and prostate cancer cell motility in vitro
  - **Foxy-5 inhibits metastases to the liver and lungs in a breast cancer mouse model (PoC)**
  - Foxy-5inhibits metastases to the lungs in a human breast cancer model in mice (PoC)

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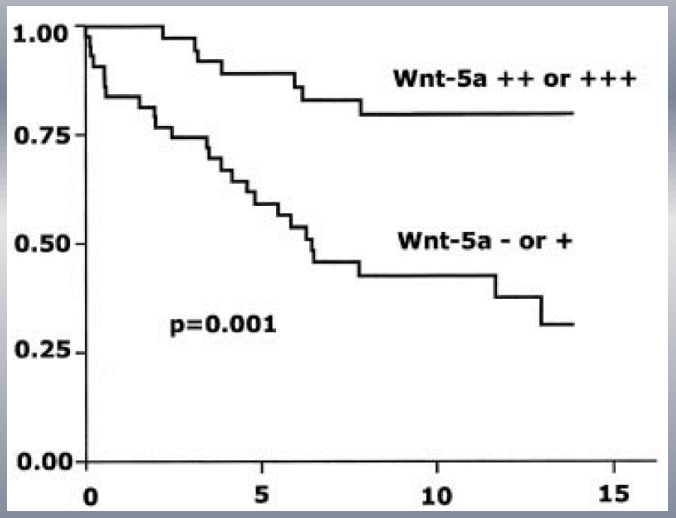
Clinical evidence of Wnt-5a role in cancer progression

Wnt-5a expression in primary tumors results in good prognosis in breast, colon and prostate cancer

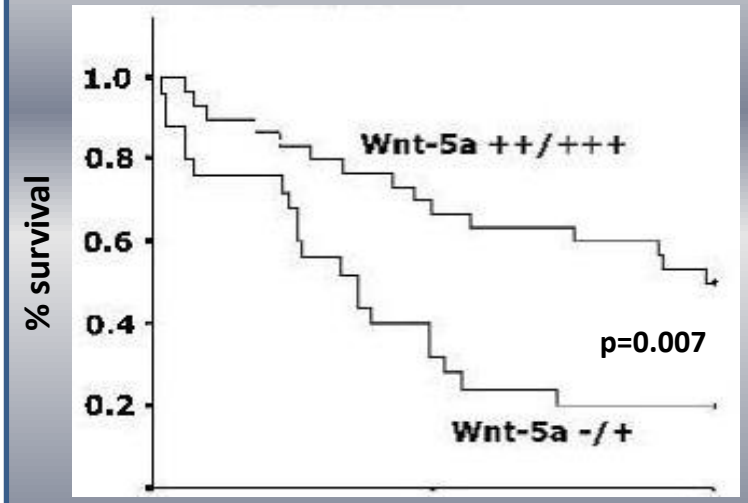
Breast cancer



N=83

Cancer Res. 2002

Colon cancer



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Cancer Res. 2005

The 4T1 mouse mammary preclinical cancer model

- **4T1 cell line is a subline derived from a spontaneously arisen tumour in a Balb/c mouse**
- **It has no endogenous expression of Wnt-5a**
- **Addition of Wnt-5a or Foxy-5 have no effect on 4T1 cell apoptosis or proliferation but impairs cell migration in vitro**
- **4T1 cells form a primary tumour already 7-10 days after inoculation into the mammary fat pad of mice**
- **Metastasizes to the lungs and liver (bone and brain – takes longer) occur via the hematogenous route and can be detected 4 weeks after cell inoculation**

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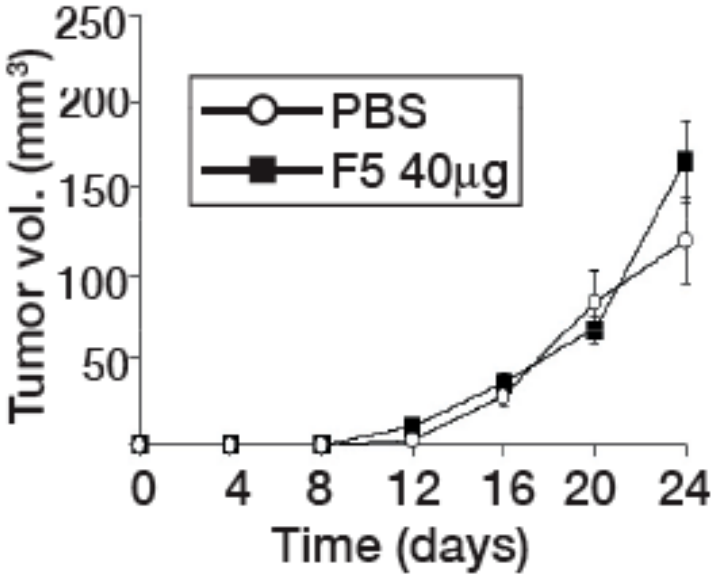
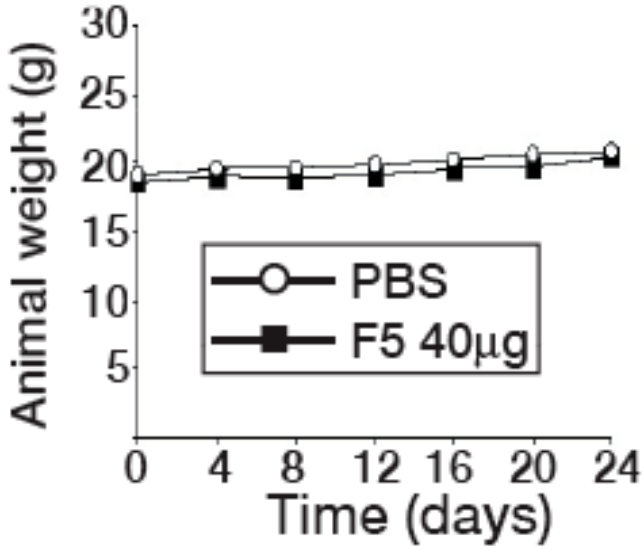
Foxy-5 has no effect on primary 4T1 tumours or animal weight

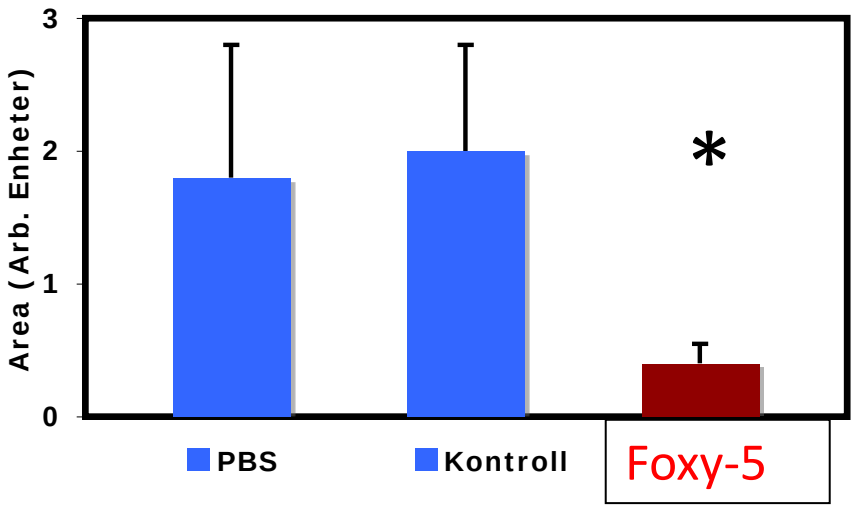




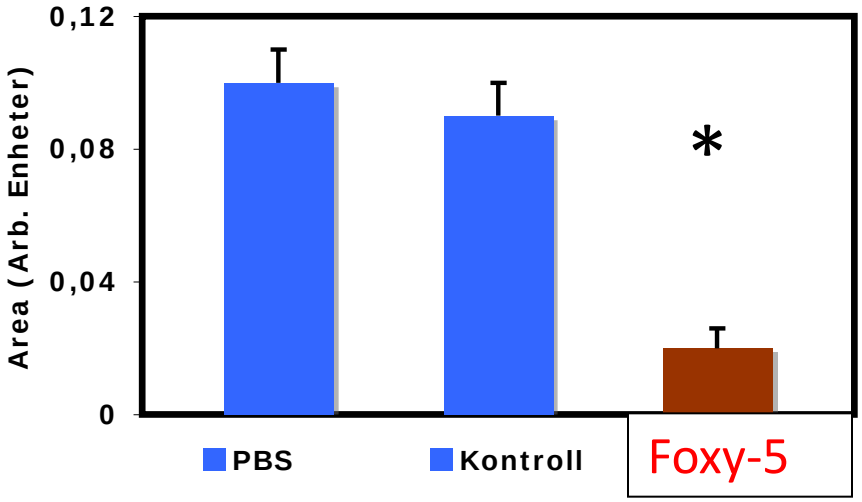
Säfholm et al., Clinical Cancer Research. 2008

Effect of Foxy-5 on formation of 4T1 breast cancer cell metastases to lungs and liver in mice

LUNGS



LIVER



* P< 0.05

Säfholm et al., Clinical Cancer Research. 2008

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New data from the laboratory

Professor Tommy Andersson has shown that Foxy-5 is inhibiting metastatic spread from a prostate cancer grown in mice.
Manuscript submitted

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Pre-clinical toxicity studies

- 4 weeks acute tox studies in rats and dogs
- Long-term toxicity studies in rats and dogs: ongoing

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Foxy 5 preclinical toxicology

- **Preparation before the clinical phase 1 study (finalized)**
  - Pilot and short term (4 weeks) dosing studies (according to ICH in two species (rats and dogs))
  - Dose levels up to 8 mg/kg in rats and 2.5 mg/kg in dogs administered daily as bolus doses for 4 weeks
  - No meaningful treatment related findings
  - NOEL of 8 mg/kg in rats and of 2.5 mg/kg in dogs
  - Kinetics revealed a clear dose response
  - No accumulation
  - t½ of approx. 0.5 hours in both species used

- **Preparation before the clinical phase II study (ongoing)**
  - 28 weeks in rats
  - 36 weeks in dogs

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Clinical development program with Foxy-5

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Phase 1 clinical program
Classical dose escalating trial with 3+3 cohort design

- **Classical Phase 1 dose escalating trial with a 3+3 cohort design in patients with metastatic solid tumors and no or low Wnt-5a expression in primary tumor**
  - Primary Objective
    - Evaluate the safety and tolerability
  - Secondary Objectives
    - Determine maximum tolerated dose (MTD) and dose-limiting toxicity (DLT)
    - Characterize the single and multiple dose pharmacokinetic (PK) profile
    - Characterize the pharmacodynamic (PD) profile
    - Assess preliminary evidence of anti-metastatic tumor activity (CTC and biomarkers)
  - Final results expected 2015

- **The dose steps are:**
  - Step 1: 0.013 mg/kg on all dosing days
  - Step 2: 0.026 mg/kg on all dosing days
  - Step 3: 0.052 mg/kg on all dosing days
  - Step 4: 0.104 mg/kg on all dosing days
  - Step 5: 0.208 mg/kg on all dosing days
  - Step 6: 0.416 mg/kg on all dosing days
  - Step 7: 0.832 mg/kg on all dosing days
  - **Step 8: 1.3 mg/kg on all dosing days**

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Biomarkers for effect of Foxy-5 in Phase 1 and 1b

- **Only patients with no or low Wnt-5a expression in primary tumour are enrolled**
  - Patient tumors are screened for Wnt5a immunoreactivity before entering the clinical trial

- **Number of circulating cancer cells are measured at day 0, 12 and 19 post-treatment**

- **Based on results from our in vitro work we also determine**
  - Blood levels NGAL and 15-PGDH before and after treatment
  - Tumor tissue levels of NGAL and 15-PGDH by IHC before and after treatment
  - Changes in gene expression in tumor tissue following Foxy-5 treatment

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Phase 1 clinical program
EudraCT no.: 2012-004200-35

- **The study is conducted at the University Hospital in Herlev and at the University Hospital Rigshospitalet at the Phase 1 Unit**
- **We have now initiated dose level 8 (is one dose level above the dose used in mouse studies)**
- **Until now no drug related toxicity to determine DLT has been observed**
- **An exploratory phase 1b study will be initiated 2015 to optimize conditions for forthcoming phase 2 study.**

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Phase 1b

An exploratory study with focus on effect

- **Primary goal is to further explore the most efficient dose of Foxy-5 for the upcoming phase 2-study. This means that we will increase the dose of Foxy-5 further.**

- **The trial will focus on potential biologic effects of Foxy-5. We will by CT scans determine the number of new metastases during treatment. Moreover, we will continue to count circulating tumor cells but add an additional method for such determinations.**

- **It will include studies on tumor biopsies and blood biomarkers in selected patients. We will determine Foxy-5 induced changes in tumor tissue gene expression. Moreover, we will analyse blood for changes in selected biomarkers.**

The goal of the phase 1b study is to obtain more information on the biological effects of Foxy-5 treatment to be used when designing the phase 2 study.

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Phase 2 Program

Overall considerations

- Select from breast-, prostate-, or colon cancer with low or no Wnt-5a cancer cell protein expression
- Select group of patients with very low or no metastatic burden
- Select patients with high-risk of later metastases development
- Select patients with a high prevalence
- Select patients with no or very few competing trials

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Phase 2 plan

- **Indication and design of phase 2 studies**
  - Clinical Advisory Board
  - Phase 1 and Phase 1b studies
  - Pre-clinical data

- **Patients with stage 3-N2 colon cancer**

Inclusion criteria:	Patients with stage 3-N2 colorectal cancer and with Wnt5a negative cancer cells
Endpoint:	Time to recurrence and overall survival
Number of patients:	2 x 100
Study design:	Randomized between standard treatment and standard treatment plus Foxy-5

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New important publication

Borcherding et al., Cancer Research, March, 2015: Paracrine Wnt5a signaling inhibits expansion of tumor-initiating cells

This could be very important as Foxy-5 is expected to be given together with chemotherapy

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WntResearch has its second drug candidate in preclinical development

Box-5

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Foxy-5

Indication	Breast cancer, colorectal cancer and prostate cancer
Classification	Peptide
MoA	Reconstruct the Wnt-5a-signaling in order to prevent formation of metastases
Goal	Develop a product with a distinct and unique MoA to be used in combination with other anti-cancer treatments
Market	> $1 billion
Present phase	Clinical phase 1
Market introduction	Potentially during 2019
IP position	Patent protection to at least 2026 (USA 2028)
Next milestone	Finalize and report phase 1 study 2015
Expected exit	At the end of phase 2 study (2016/17)

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Why invest in WntResearch?

- **Foxy-5 is a truly innovative, high-quality asset in cancer**
- **"First in class therapy for mimicking the Wnt-5a"**
  - Represents a paradigm shift in cancer treatment
  - Directed against metastasis - the main factor of death in cancer
- **Lead program and technical validation by the Eurostars program**
- **Cost effective development**
  - An experienced management team
  - Slim and focused business and virtual set-up
- **Simple business model with manageable exit costs**
  - Phase 1 during 2013-15
  - Phase 1b 2015
  - Phase 2 during 2015-17
- **Transparent and easy exit strategy within a period of 3-4 years**
  - Dividends in the event of licensing of Foxy-5
  - Capital gains on the case of M & A

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Thank you for listening…

… any questions?

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