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Cyspondin platform technology

A protein-conjugate platform that selectively targets LGR expressing cells

Cyspondin Platform Technology

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A protein-conjugate platform that selectively targets LGR4/LGR5/LGR6 expressing cells

Supports development of molecules that can deliver:

- A cargo to multiple types of receptors at the same time
- Different types of cargo (MMAE, deruxtecan, exectecan…)
- Possibility of two different types of cargo on the same molecule
- Molecules that kill the stem cells in many types of solid tumor and hematologic malignancies
- Molecules that support regeneration of normal stem cells

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Cyspondin platform introduces unique features to the field

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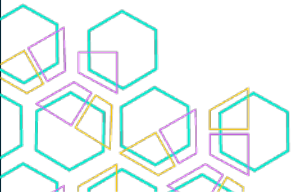
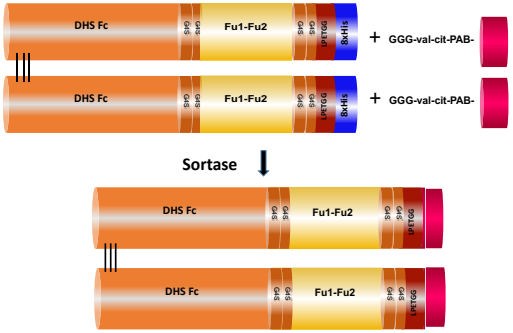
- Uses a **natural ligand** to target cargo to **LGR4, LGR5 and LGR6** receptors
- Potential to **target all these LGR** receptors simultaneously
- **Markedly different pharmacokinetics** compared to antibody-drug conjugates
- Cyspondin-based drugs are **half the size of an antibody**
- **Payload dose is ~2.5-fold higher** than ADCs
- Relative to ADCs, **much higher doses are tolerated permitting deep tissue penetration** and saturation of LGR4, LGR5 and LGR6 receptors
- Short half-life permits very intense **weekly repeated** rapid loading of drug into target tissues
  - ➢ Results in **much less systemic exposure to free cargo** due very low plasma levels



Novel platform drug delivery

Cyspondin - LGR - Platform Technology



- **Sortase reaction** adds cargos (represented in red) only at the C-terminal site and no other sites
- Cargo is coupled via a val/cit-PAB-cargo cleavable linker
- Efficiency of sortase reaction: >85%
- Possibility of loading multiple types of cargo (cytotoxins, PROTACs, small molecules that support regeneration)

Warheads: MMAE, deruxtecan, exatecan

Fu1-Fu2 **Target: high affinity for LGR4, LGR5, LGR6**

MW of dimer 85,284 Da

Precise loading of cargo at one site per chain

Background Platform Rationale

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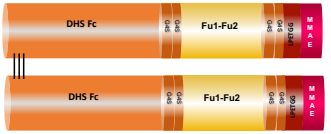
- All rapidly dividing epithelial are sustained by primitive stem-like cells
- The **LGR4, LGR5 and LGR6** family of receptors **mark active stem cells**
  - Validated by >100 publications using *in vitro* and *in vivo* biologic systems
  - Validated in >50 molecular and lineage tracing systems
- **LGR5** in particular is over-expressed in the stem cells of **many common types of cancer** including colon, gastric, endometrial, ovarian, lung, breast, skin, etc
- **Cyspondin platform** uses the binding domain of a normal ligand to **selectively deliver cargo to LGR4, LGR5 and/or LGR6** positive stem cells.
- After binding to an LGR the **cargo is rapidly endocytosed and released intracellularly**
- LGR5 clinically and commercially **validated target**
  - ➢ **Genmab paid Merus $ 8 billion for the first LGR5-targeting drug that has reached Phase III trials**

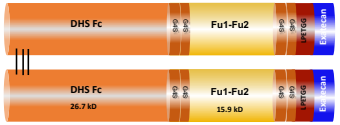
Focus of current development based on Cyspondin platform

Use of LGR targeting capacity to deliver:

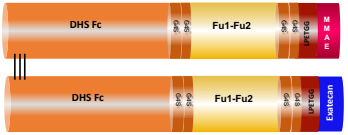
- Two copies of tubulin inhibitor MMAE to cancer stem cells
- Two copies of a Top1 inhibitor (exatecan or deruxtecan) to cancer cells
- Development of molecules that deliver two different types of toxins at the same time to cancer cells



MMAE warhead



Exatecan or deruxtecan warhead



Two types of warheads

Lead Candidate: CYMIRAFEN

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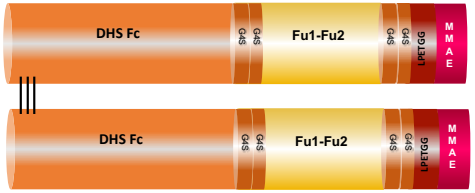
A protein-conjugate cancer therapeutic: **selectively targets LGR4, LGR5 and LGR6 cells** in multiple types of cancer

<u>Cellular targets:</u>

- LGR4, LGR5 and LGR6 receptors uniquely expressed at high levels in cancer stem cells
- Binds to all 3 stem cell receptors simultaneously



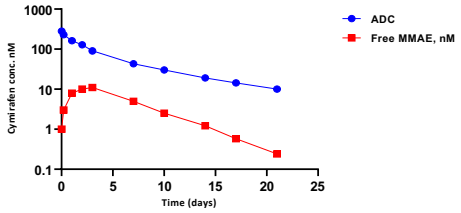
Warhead: MMAE conjugated via cleavable linker

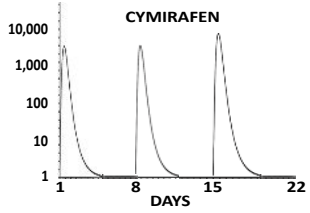
Extremely potent: IC_{50}s in high pM - low nM range for many types of cancer

Potential **treatment for**: gastric, esophageal, colon, endometrial, ovarian, pancreatic, prostate, skin cancers and AML

Pharmacokinetic advantages of cymirafen vs. ADCs

Based on allometric scaling from rat data, cymirafen will deliver extremely intense short-duration exposures that result in rapid loading of MMAE into tumor but only brief exposure to free MMAE in plasma





- **Unique short half-life** and reduced free plasma MMAE on a weekly schedule

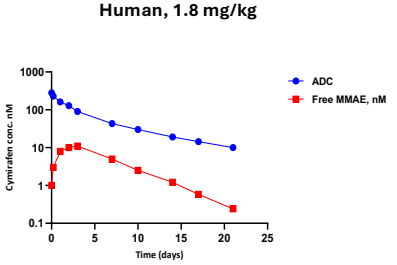
  Cymirafen attains the **very high plasma** concentrations needed to access all the cells in a tumor express the LGR4/LGR5/LGR6 receptors

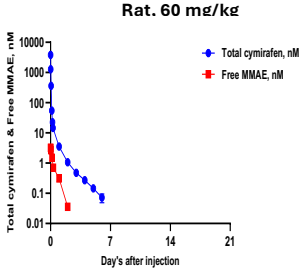
  Intense high level but short-term exposure for tumor produces **rapid loading of MMAE** into tumor cells

- **Low free MMAE plasma levels** and short MMAE half-life markedly reduces exposure of normal tissue permits injection of extremely high doses
- Cymirafen has ~2.5-fold higher payload dose (moles of MMAE/tolerated dose)

ADCs have a problem that is solved by Cymirafen

- Human doses of ADCs are small (1.2 – 4.5 mg/kg/3 wk) because they are not tolerated
- ADC doses are too small to penetrate deeply into tumor
- Plasma concentrations are too low to saturate all receptors on those cells the ADC can reach
- Neurotoxicity occurs in up to 50% of patients because MMAE ADCs produce very long duration exposures to free MMAE in plasma that paralyzes tubulin-mediated neuronal transport
- **Cymirafen is much better tolerated because it yields little free MMAE in the plasma**





Cymirafen - Molecular Advantages

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- **Cymirafen is extremely potent**: IC_{50} values 0.5 – 10 nM in cell line panels in 2D and 3D spheroid cultures
- **Cymirafen is highly selective** for cells that express LGR5
  - Extensive validation that cell kill is dependent on LGR5 expression both in vitro and in vivo
- **Efficacy in multiple human xenograft models**:
  - Documented efficacy in colorectal, gastric, ovarian cancers and neuroblastoma thus far
  - Efficacy data sufficient for IND
- **Favorable pharmacokinetic profile** – PK in mice and rats supports weekly dosing
- **Favorable toxicology profile**:
  - HNSTD in rats is 8 times higher that all approved ADCs

Unique target and cell-validated basis for selectivity

Cymirafen – examples of xenograft efficacy data

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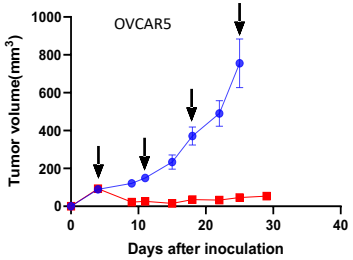
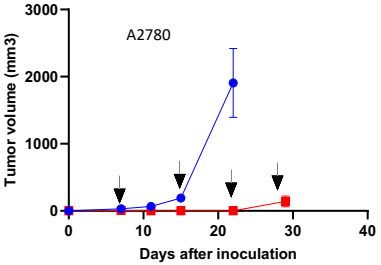
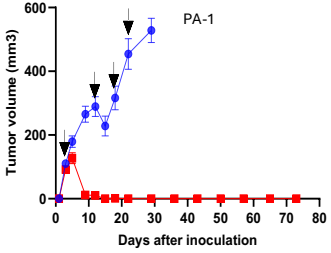
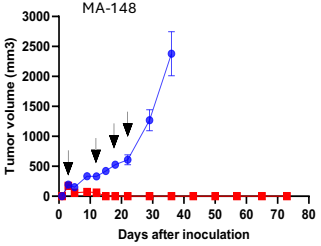
Examples of curative efficacy in ovarian cancer









For all experiments

N =16 tumors/group

PBS control group

Cymirafen 85.4 mg/kg

Cymirafen - Developmental Advantages

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Regulatory

- Cymirafen is an **ADC-like biologic** so it exploits the extensive experience with development of MMAE ADCs
- Ready for **meeting with FDA**, contracting for production of **non-GMP drug** and **non-GLP toxicology studies**

CMC

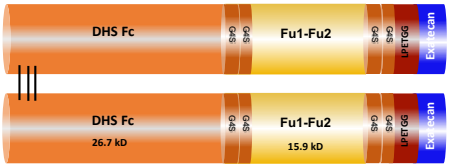
- Cymirafen is a **robust and stable protein**
- Purification uses standard 2-step Ni-NTA capture and ion exchange technology
- High level production by **stable CHO clones** has been established

Intellectual property

- Patent family 1: Issued patents in US, CA, DE, FR, DK, IE, NL, NO, SE, CH, UK and US pending divisional (filed Feb 16, 2017)
- Patent family 2: Pending applications in US, CA, EP, JP, AU, CN, KR (filed Feb 25, 2023)

Next drug to be developed - Exarafen

- Same backbone as cymirafen but with a different warhead – exatecan
- Exatecan has a different mechanism of action (targets TOPI)
- Exarafen builds on success of cymirafen



- Exarafen will have greater activity the cymirafen in some types of cancer and less in others
- Will provide further proof of principle that platform can be used for create multiple types of drugs
- Provides opportunity to target same receptors but with different warheads to overcome drug resistance

Precise matching of drug with type of cancer

Advantages of cymirafen over LGR targeting ADCs

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- **Uses natural ligand** for targeting - **low immunogenicity risk**
- **Cymirafen** can **target** all 3 members of the **LGR family of cancer stem cell receptors** (LGR4, LGR5 and LGR6) and their co-receptors ZNRF3/RNF43 at the same time, whereas an ADC can target only a single receptor type
- **Hits 3 targets** - can target cells with low expression of one type of the LGR or co-receptor but substantial expression of another
- Bispecific and bivalent binding of cymirafen to LGR4, LGR5 or LGR6 and their **co-receptors** favors **selectivity and enhanced rate and extent of internalization**
- Ability to bind to ubiquitin ligases independently of LGRs permits **targeting of tumors that uniquely over-express ZNRF3 and RNF43.**

Cymirafen solves a major MMAE ADC toxicity problem

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- ADCs that use MMAE as a warhead have low efficacy and high toxicity
- Their efficacy is low because only very low doses are tolerated. Doses are so low that:
  - There is poor tumor penetration
  - Concentrations attained do not saturate the target receptors on cells that are reached
- Only low doses are tolerated because these ADCs cause severe neurotoxicity
- Severe neurotoxicity is due to the fact that they maintain continuous high plasma concentrations of free MMAE for long periods of time (3 weeks or more).
- Their doses are so low that there is poor tumor penetration and concentrations attained do not saturate the target receptors.
- In contrast, cymirafen can be given in very large doses that produce short-term exposure to very high plasma concentrations once a week
  - Very rapid pulse loading of large amounts of MMAE into tumors
  - Very short duration exposure to low levels of free plasma MMAE

Cymirafen solves a major ADC problem by virtue of its fundamentally different pharmacokinetics

Cymirafen Summary and Highlights

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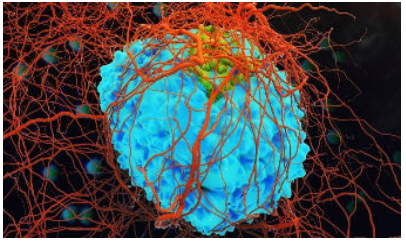
- Specifically attacks **LGR pathologic cells** - critical target
- Novel concept exploiting **affinity and specificity of RSPO1**
- **Very potent,** 0.5 – 10 nanomolar potency against many solid tumors
- **Selective LGR5-dependent killing** in vitro and in vivo
- **Kills stem cells** in spheroid assay (**multiple tumor types)**
- **Limited toxicity** at effective doses on clinically-relevant dose schedule
- **~2.5-fold more MMAE delivered per dose**
- **Intense loading of MMAE into tumor without long duration free MMAE exposure**
- **High level production** possible in CHO clones
- Limited complexity of **CMC workflow**
- Well paved **regulatory route**



LGR competitive landscape

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Candidate	Modality & Target	Company	Indications	Trial phase & status	Select efficacy readouts	Key safety notes
CNA3103	Autologous **CAR-T LGR5**	Carina Biotech	Metastatic colorectal cancer	Phase 1/2a – recruiting(Australia; global expansion planned)	— (dose-finding/early exploration)	Typical lymphodepletion + CAR-T AEs expected; detailed safety pending
BNC101	mAb **LGR5**	Bionomics	Metastatic colorectal cancer (mono ± chemo)	Phase 1 – terminated early; study closed	— (no mature public efficacy dataset from FIH)	—
Petosemtamab (MCLA-158)	Bispecific IgG1 **EGFR × LGR5**	Genmab / Merus	Head & neck SCC (r/m), incl. 1L PD-L1+(with pembrolizumab); also studied across EGFR-dependent tumors incl. mCRC	Phase 3 (registration)	1L HNSCC (petosemtamab + pembro, Phase 2): ORR 63–67% (n≈43 evaluable); 12-mo OS ~79%; median PFS ~9.0 mo (cutoff Feb 27, 2025).	TEAEs in all pts; ≥G3 TEAEs ~40% in combo Phase 2; manageable EGFR-class AEs (e.g., rash, hypomagnesemia) and infusion reactions; low discontinuation.

Genmab paid Merus $ 8 billion for petosemtamab (EGFR x LGFR5 mAb) in Phase III trials

Next steps - *pathway to the clinic and capital requirements*

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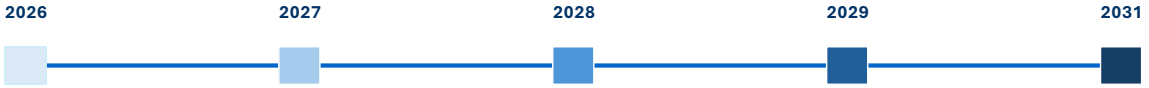

In Development
Dr. Howell's lab at UCSD
Funded by Clayton

Preclinical Studies
CMC and assay validation
Monkey PK & Safety IND
Budget : $5M

Lead Molecule IND & Phase 1 initiation
Platform Expansion
Validation & further platform development
Budget : $12M

Lead Molecule Phase 1 completion
Second compound pre-IND studies
Cumulative budget: $30M

Lead Molecule Phase II and expansion
Cumulative budget: $85M

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