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# World ADC 2023 – targeting the folate receptor rises from the ashes

Jacob Plieth

## Zymeworks, Profoundbio, Elucida and Immunogen itself piggyback on Elahere's success to develop a better antibody-drug conjugate.

Drug development ideas come and go, but few oncology targets have experienced a rise from obscurity to rival that of folate receptor alpha. Spurred by the approval of Immunogen's Elahere and the $650m up-front Bristol Myers Squibb gave Eisai for a similar asset, the industry pipeline now features several clinical projects with this mechanism.

It seems that most are banking not only on the FRα target but also on the way to hit it: antibody-drug conjugates (ADCs), Elahere's modality, abound. Still, Elahere is far from perfect, with ocular toxicity likely holding back widespread adoption, and this week's World ADC conference in London heard of numerous companies trying to develop a better Elahere.

Chief among these, it must be stressed, is Immunogen itself. A phase 1 trial of the company's Elahere follow-on, IMGN151, dosed its first patient in January, Olga Ab, Immunogen's director of clinical development, told the conference.

IMGN151 features a number of improvements: it binds two distinct FRα epitopes and boasts a next-generation payload and novel linker. It has a longer half-life, increased payload delivery and higher exposure, and preclinical data suggest that it has double Elahere's affinity for FRα; one result is an improved bystander killing activity, said Ab.

### ADC buzzword

"Bystander activity" was one of the most frequently mentioned phrases at World ADC. The phenomenon signifies an ADC's ability to hit not only the target cells but also those in the vicinity, irrespective of whether they display the desired antigen; it is why Astrazeneca/Daiichi Sankyo say Enhertu works in patients who have vanishingly low Her2 levels.

A similar pitch was made at the conference by Zymeworks, which recently disclosed a new anti-FRα ADC coded ZW191. This is based on a novel antibody and novel linker, and its bystander killing ability should enable low FRα-expressing cancers to be targeted. IND filing is planned next year.

All speakers confidently called FRα a "validated target", and it is clear that Elahere is the drug that validated

it. Earlier FRα had been consigned to the scrapheap with the blow-up of Endocyte's vintafolide in 2014.

In a sign of how important big pharma now considers FRα, in 2021 Bristol licensed Eisai's ADC MORAb-202, now known as farletuzumab ecteribulin, for an extraordinary $650m up front. The asset will feature in a clinical abstract at next month's AACR meeting, which will also include preclinical data from a separate ADC, Astra's previously undisclosed AZD5335.

Some biotech investors are also closely following Sutro, which controversially claims that its lead asset, the anti-FRα ADC luveltamab tazevibulin, can hit twice as many ovarian cancer patients as Elahere – US accelerated approval limits Elahere's ovarian cancer label to patients who are FRα positive.

Luvelta's commercial path is via an accelerated approval, and Sutro hopes to start a registrational trial this quarter. However, this strategy depends crucially on Elahere, whose own confirmatory trial, Mirasol, has hit the required number of PFS events and is due to read out in May. If this results in full approval for Elahere the accelerated pathway would likely close for luvelta.

| Antibody-drug conjugates targeting folate receptor alpha | | | |
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| **Project** | **Company** | **ADC payload** | **Status** |
| Elahere (mirvetuximab soravtansine) | Immunogen | DM4 maytansinoid (microtubule inhibitor) | Accelerated approval for 2nd to 4th-line FRα +ve ovarian cancer |
| Farletuzumab ecteribulin (MORAb-202) | Bristol Myers Squibb/ Eisai | Eribulin (microtubule inhibitor) | Ph2 ovarian & NSCLC (FRα unselected) |
| ELU001 | Elucida | Exatecan "C'dot" | Ph1/2 in FRα overexpressing solid tumours |
| PRO1184 | Profoundbio | Exatecan (topo I inhibitor) | First ph1/2 (FRα unselected solid tumours) patient dosed Q4 2022 |
| IMGN151 | Immunogen | DM4 maytansinoid (microtubule inhibitor) | First ph1 (FRα unselected ovarian cancer) patient dosed Jan 2023 |
| Luveltamab tazevibulin (STRO-002) | Sutro Biopharma | Hemiasterlin (microtubule inhibitor) | Ph1 in ovarian cancer with minimum level of FRα expression |
| BAT8006 | Bio-Thera Solutions | Exatecan (topo I inhibitor) | Ph1 in FRα unselected solid tumours |
| AMT-151 | Multitude Therapeutics | Unclear | Ph1 in FRα unselected solid tumours |
| ZW191 | Zymeworks | Camptothecin (topo I inhibitor) | Preclinical, IND filing 2024 |
| MBK-103 | Mablink | Exatecan (topo I inhibitor) | Preclinical, AACR poster |
| AZD5335 | Astrazeneca | Topoisomerase I inhibitor | Preclinical, AACR poster |
| *Source: clinicaltrials.gov & company disclosures.* | | | |

The World ADC meeting was timely not only because of the resurgence of FRα but also because ADCs were put firmly back on the agenda by Monday's $43bn takeover of Seagen by Pfizer.

And it was Profoundbio, a private Seattle-based biotech founded by former Seagen employees, that claimed "potential best-in-class" status for its anti-FRα ADC PRO1184. This uses a novel linker to reduce toxicity and widen the therapeutic window, and has a drug-to-MAb ratio of eight, enabling increased payload delivery per internalisation.

A recently begun all-comers study at US and Chinese hospitals might have a trials-in-progress abstract at Asco, Profoundbio's chief operating officer, Tae Han, told World ADC.

A similar claim was made by Gregory Adams, chief scientific officer of another private biotech, Elucida Oncology. Elucida's ELU001 is an ADC using the company's C'dot technology, which generates "ultra small"

constructs that carry up to 10 times more targeting moieties and up to 10 times more payload than traditional ADCs.

Like PRO1184, ELU001 is claimed to have reduced toxicity and to target cancers not normally thought of as high-FRα expressing, for instance paediatric AML and brain tumours. A phase 1 trial has seen one confirmed partial response in an FRα-low endometrial cancer patient, among 14 treated, said Adams; data are possible at Esmo.

The potential for improved tolerability is a live issue given Elahere's boxed warning of ocular toxicity, though in a separate World ADC session Immunogen's medical director, Michael Method, said this could increasingly be mitigated with steroid eye drops. Nevertheless, "we hope others can improve on Elahere just like we're trying to do with IMGN151", he said.

*The table in this story has been updated.*