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Interview – How AC Immune could finally (dis)prove the amyloid hypothesis

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The failure of just about everything thrown at Alzheimer's disease so far has not deterred the industry. And last year's Nasdaq float of AC Immune – which claims to have the broadest Alzheimer's pipeline in the business – shows that investors, too, remain enthusiastic.

AC's chief executive, Andrea Pfeifer, insists that the Swiss group really is doing things differently. The keys to success? Accurate diagnosis and the ability to dose patients at high enough levels, she tells *EP Vantage*. What is more, she reckons she could have foreseen the failures of at least three competing Alzheimer's projects.

Still, Ms Pfeifer remains an ardent believer in the amyloid hypothesis, and says the problem here is not the target but the lack of a therapeutic window. "[Elan's] bapineuzumab was highly toxic," she states, pointing to a high incidence of vasogenic oedema (ARIA-E), which was confirmed as a class effect in an early trial of Biogen's aducanumab.

Meanwhile, recent setbacks with Merck & Co's Bace inhibitor verubecestat could have been foreseen given that Bace is involved in amyloid-beta accumulation, so once the protein has formed inhibiting it is useless, Ms Pfeifer says.

"We are not in Bace – this was a very conscious decision," she says, adding that Bace also suffers from a lack of specificity, hitting 80 proteins in addition to amyloid precursor.

The failure of Lilly's solanezumab, however, was more mysterious. "I'm convinced that if [Lilly] had given double or triple the dose – which they could have done, because the side effects were pretty minor – I think they would have seen something," says Ms Pfeifer. "Why they didn't do it I don't know."

Crenezumab and the therapeutic window

AC is perhaps most famous for being the licensor of crenezumab, which along with the Morphosys-originated gantenerumab represents Roche's two-shot bet on the amyloid-beta hypothesis.

Perhaps less well known is that AC also licensed to Roche the anti-tau MAb RG6100, while its anti-tau vaccine ACI-35 is partnered with Johnson & Johnson. One of its imaging agents, for detecting alpha-synuclein in Parkinson's disease, is licensed to Biogen.

Diagnostics are a major part of AC's clinical, if not commercial, strategy, as evidenced by the fact that crenezumab's pivotal trials require evidence of amyloid-beta in the cerebrospinal fluid to be confirmed by immunoassay or PET scanning.

This points to another failure of competing amyloid-beta-targeting studies, which Ms Pfeifer insists used the wrong population, possibly too broad and definitely too late in the course of Alzheimer's progression, she reckons: "You couldn't start early enough because you didn't have a diagnostic."

But as well as imaging-assisted early dosing, Ms Pfeifer says you need to have a compound with a decent therapeutic window, which according to her calculations aducanumab, gantenerumab and bapineuzumab might not have.

Why not? Largely because they are IgG1 MAbs, whereas crenezumab is IgG4-based, meaning that it "clears the brain without inflammation. With a mechanism of action on oligomers... it does not attack vascular amyloid-beta. ARIA-E is linked to vascular amyloid-beta perforation."

Characteristics of selected Abeta-targeting MAbs				
Compound	**Company**	**Isotype**	**Dose***	**ARIA-E incidence**
Crenezumab	AC Immune/Roche	IgG4	60mg/kg	<0.2%
Aducanumab	Eisai/Biogen	IgG1	3-10mg/kg	35-41%
Gantenerumab	Morphosys/Roche	IgG1	1.5-17.1mg/kg	10.0-22.9%
Solanezumab	Lilly	IgG1	5.7mg/kg	1%
BAN2401	Eisai/Biogen	IgG1	2.5-10mg/kg	0%
Bapineuzumab	Elan/J&J	IgG1	0.5-1mg/kg	~10%
*Source: AC Immune, scientific papers; *calculated from Clinicaltrials.gov.*				

To underline her point Ms Pfeifer says AC has dosed crenezumab at 60mg/kg – severalfold higher than competing agents – with no relevant side effects. She says almost all the new competing anti-Alzheimer's antibodies, though none targeting amyloid-beta, are IgG4s: "I think that's what our contribution was to the field."

It is an open question why Eisai/Biogen's IgG1 MAb BAN2401 has not been associated with ARIA-E, as is the groups' apparent reluctance to dose higher.

And another intriguing though now hypothetical question is whether bapineuzumab in an IgG4 form would have had a cleaner profile, and could at a high enough dose have shown efficacy (*Axovant scraps Alzheimer's bid – now back to the amyloid hypothesis, September 26, 2017*).

Multiple shots

In addition to amyloid-beta AC is targeting tau, with a MAb, small molecule, vaccine and diagnostic. The imaging agent "allows us to discriminate between the different forms of tau", Ms Pfeifer says, stressing that it is still unclear how many prodromal patients have this protein, or when it develops in the course of disease.

And she thinks only Lilly has tracers to pinpoint amyloid-beta and tau, which if true is surprising given the complexity of Alzheimer's. "Do we think that with one shot we are going to cure Alzheimer's?" she asks. "No, it doesn't work like that."

While it will be some time before AC's theories will be proved or disproved – crenezumab's pivotal trials start reading out in 2020 – Ms Pfeifer is convinced that patient profiling, not genetically but at a protein expression level, is set to grow in importance in Alzheimer's.

"We are not precise enough," she says. "You should look at our company as [being in] a situation where oncology was 30 years ago."

This story was amended to reflect the correct code for the Roche anti-tau MAb.

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