

Can new drug delivery systems solve the VEGF-injection dilemma?

Associate Professor Ilva Rupenthal
Director of the Buchanan Ocular Therapeutics Unit
Department of Ophthalmology
New Zealand National Eye Centre
Faculty of Medical and Health Sciences
The University of Auckland


Biosimilars

► a biologic medical product similar to an already approved product in terms of quality, safety and efficacy and marketed by an independent company following expiry of the original product patent

Company	Asset	Target(s) / API(s)	Approach	Category	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
Cellgene	PF032 (Lucentis biosimilar)	VEGF-A	Ab Fragment (IV)	BLA Reg. No. MDA Reg. 22					
Sanofi / Regeneron	SB11 (Lucentis biosimilar)	VEGF-A	Ab Fragment (IV)	Phase 1/2 (Phase 3 pending)					
Novartis	SUP-0333	VEGF-A	Ab Fragment (IV)	Phase 1/2 (Phase 3 pending)					
PFizer	PF032 (Lucentis biosimilar)	VEGF-A	Ab Fragment (IV)	Phase 1/2 (Phase 3 pending)					
Novartis / FALCA	Novus (Lucentis biosimilar)	VEGF-A	Ab Fragment (IV)	Phase 1/2 (Phase 3 pending)					
Novartis	Novus (Lucentis biosimilar)	VEGF-A	Ab Fragment (IV)	In preclinical studies					


Ziv-aflibercept (Zaltrap; Sanofi-Aventis)

Mvasi (Amgen, Allergan); Zirabev (Pfizer); Versavo (Dr Reddy's)





Currently approved for wet AMD

Company	Asset	Target(s) / API(s)	Approach	Category	Phase 1	Phase 2	Phase 3	Phase 4
Novartis / Regeneron	Lucentis (anti-VEGF)	VEGF-A	Ab Fragment (IV)	Approved				
Novartis / Regeneron	Macugen (anti-VEGF)	VEGF-A	Ab Fragment (Intravitreal Implant)	Phase 3 data not 2D				
Regeneron / Bayer	Eylea (anti-VEGF)	VEGF-A, PlGF	Ab Trap (IV)	Approved				
Regeneron / Bayer	Eylea (anti-VEGF)	VEGF-A, PlGF	Ab Trap (IV)	Approved				
Novartis	Novus (anti-VEGF)	VEGF-A	Ab Fragment (IV)	Approved Oct 10				
Novartis	Novus (anti-VEGF)	VEGF-A	Ab Fragment (IV)	Limited use, granted				
Novartis	Novus (anti-VEGF)	VEGF-A	Ab Fragment (IV)	Limited use, granted				
Novartis	Novus (anti-VEGF)	VEGF-A	Ab Fragment (IV)	Limited use, granted				
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Does size really matter?

	Brolucizumab (Beovu)	Ranibizumab (Lucentis)	Aflibercept (Eylea)	Bevacizumab (Avastin)
MOA	Anti-VEGF-A	Anti-VEGF-A	Anti-VEGF-A / PlGF/VEGF-B	Anti-VEGF-A
Type	Single-chain AB fragment	Monoclonal AB fragment (Fab)	VEGF1/2-Fc Fusion protein	Monoclonal AB (IgG1)
MW (kDa)	26	48	97-115	149
t _{1/2} (days)	4.5/0.25	7.1/0.25	11/6.7	9.8/21
Clinical dose (mg)	6	0.5	2	1.25
Relative number of molecules per injection	11.2-13.3	0.5-0.6	1.0	0.4-0.5
kD for VEGF ₁₆₅ (pM)	28.4	46	0.5	58

KODIAK Let's make it bigger then!

ANTIBODY
IgG1 selected immune effector function


BIOPOLYMER
Oxidative cross-linking, high molecular weight, phosphocholine polymer

CONJUGATE
Antibody and biopolymer covalently bound via single site-specific linkage

FORMAT	ANTIBODY FRAGMENT (BROLUCEPT)	FUSION PROTEIN (EYLEA)	ANTIBODY-BIOPOLYMER CONJUGATE (KODIAK PLATFORM)
Structure			
Size	48 kDa	95 kDa	150 kDa
Dose per dose	1x	2x	7x
Ocular half-life	1x	1.5x	2x

SCHEMATIC REPRESENTATION OF THE THERAPEUTIC RETREATMENT WINDOW

→ Currently enrolling for Phase II DAZZLE study; dosing every 4-5 months



MOLECULAR partners Let's make it bigger then! Allergan

MONOCLONAL ANTIBODIES

- Large size: 150 kDa
- Complex architecture: 4 proteins with 12 domains
- Target binding via flexible surface loops (CDRs)

DARPin® Protein(s) Designed ankyrin repeat proteins

- Small size: 15 kDa (1/10 of monoclonal antibody)
- Simple architecture: 1 protein with 1 domain
- Target binding via rigid surface structure

SCALE

Multi-DARPin® product candidate

- High affinity and specificity
- Low immunogenicity potential
- Tunable half-life

→ active at lower concentration
→ 13 days (vs. 7.2 days for Lucentis)


Abicipar-pegol

MW 34 kDa

but high rates of intraocular inflammation

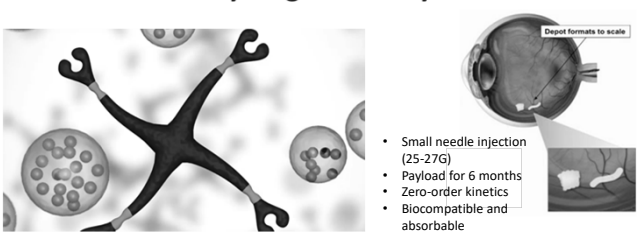
REACH 10.4%
CEDAR 15.3%
SEQUOIA 15.3%

→ Altered manufacturing process for more purified product



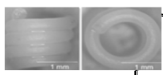

Ocular Therapeutix **REGENERON**

Hydrogel delivery



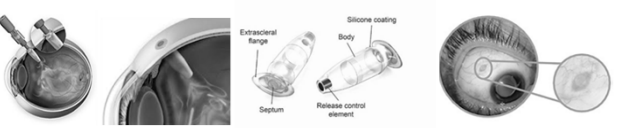
- Small needle injection (25-27G)
- Payload for 6 months
- Zero-order kinetics
- Biocompatible and absorbable

Depot forms to scale

FORSIGHT VISION 4 **Genentech**

Port delivery system




3.5 mm scleral incision; 20 µl fill volume; semipermeable titanium membrane; Fick's law of diffusion

LADDER (Phase 2): 220 patients; 10, 40 and 100 mg/ml of Lucentis (vitreous hemorrhage initially 50%)
Primary endpoint (required refill): 8.7, 13 and 15 months respectively


ARCHWAY (Phase 3): 360 patients; 100 mg/ml; mandatory refill every 6 months

"Simplicity is the ultimate sophistication"



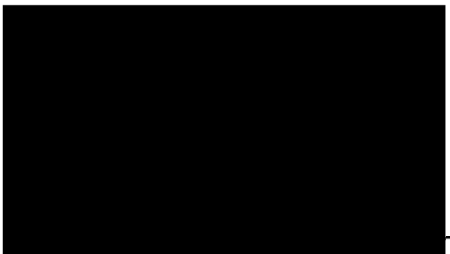

REGENXBIO **CLEARSIDE BIOMEDICAL**

Suprachoroidal delivery



AAV vector

Carries coding sequence for soluble mAb fragment against VEGF

Thank you



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