TechEx.in is a Regional Tech Transfer Office supported by:

Ranibizumab

Technology from the group of **Anurag Rathore** at **Indian Institute of Technology, Delhi, India**

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About Ranibizumab

Ranibizumab is a **recombinant humanized** monoclonal antibody and **VEGF-A antagonist**

- **Originator / reference product:** Lucentis, was marketed by Genentech (Roche)/Novartis, approved by the USFDA in June 2006 and by EMA in Jan 2007. The patents on Lucentis **expired** in the **US in June 2020** and will expire in **Europe in 2022.** (Source: GaBI Online)

- **Indications:** Used in treatment of neovascular (wet) **age-related macular degeneration (wAMD),** Macular edema following retinal vein occlusion (RVO), Diabetic macular edema (DME), Diabetic retinopathy (DR) and Myopic choroidal neovascularization (mCNV).

Market and Industry Overview

Market:

The global age-related macular degeneration (AMD) market stood at $ 1.58 billion in 2020 and is projected to reach **$ 2.64 billion by 2026, growing at CAGR of 8.93%** between 2021 and 2026. (Source: EMR)

Industry players:

- **Global:** Genentech, Novartis
- **India:** Intas

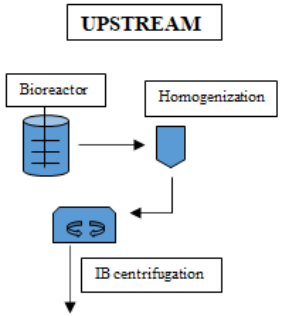
The Opportunity: Why you should be interested?

- **Market interesting**: **AMD Affects nearly 8.7% of the worldwide population,** and the numbers are projected to increase to around 196 million in 2020. Projected number of people with the disease is around **196 million in 2020, increasing to 288 million in 2040**. (Source: All About Vision)
- **Cost still high:** Approximately**, 51% of the patients on VEGF therapy dropout of therapy** after initial injections. The most common reason is non-affordability of the injection followed by no improvement in vision. (Source: The Indian Express).

Price point Global	**Price point India**
• Razumab: 2.3mg Injection @ ~ $ 270 • Lucentis: 0.5 mg injection @ ~$ 1120	• Razumab: injection $130 • Lucentis (Branded Accentrix): injection $320

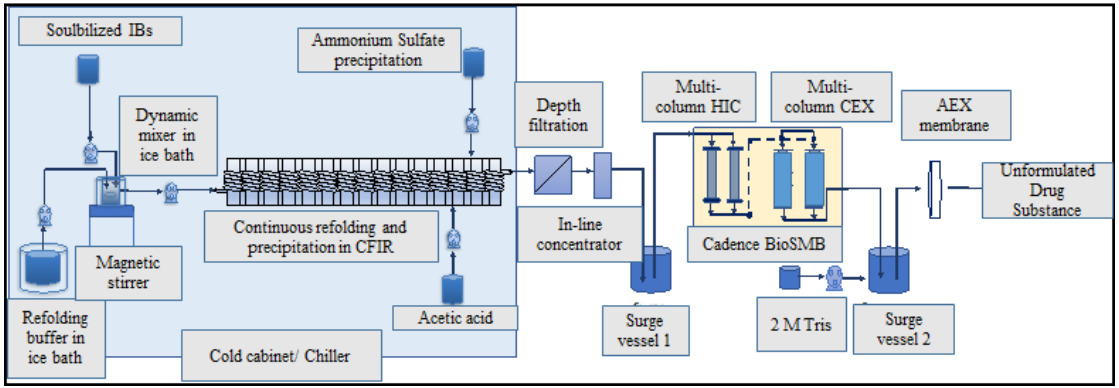
- **Industry not yet crowded: 1st ever Biosimilar of Ranibizumab**- 'Razumab' launched by Intas Pharma in 2015. Few players globally.
- **New indications:** A 2021 survey of Indian vitreoretinal specialists showed progressive trend favouring ranibizumab-biosimilar over bevacizumab-biosimilar.
- **Opportunities for process innovations to reduce costs: Novel continuous processing platform** results in reduction in Cost of Manufacturing **by 80% for clinical** and **75% for commercial production**.

The Technology Offering – Ranibizumab Biosimilar



Parameters	Responses
Titer of final purified product	0.2 g protein/ L reactor
Purification yield (HIC to AEX)	75 %

DOWNSTREAM



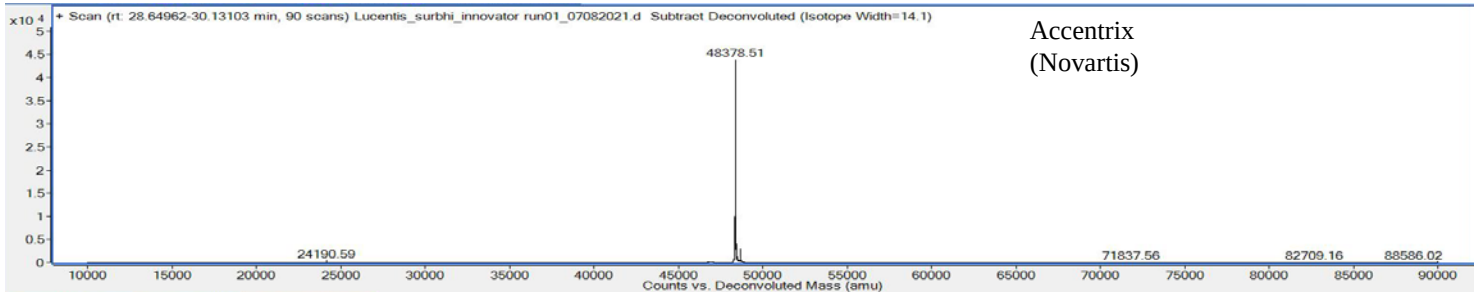
Key Highlights of the Offering

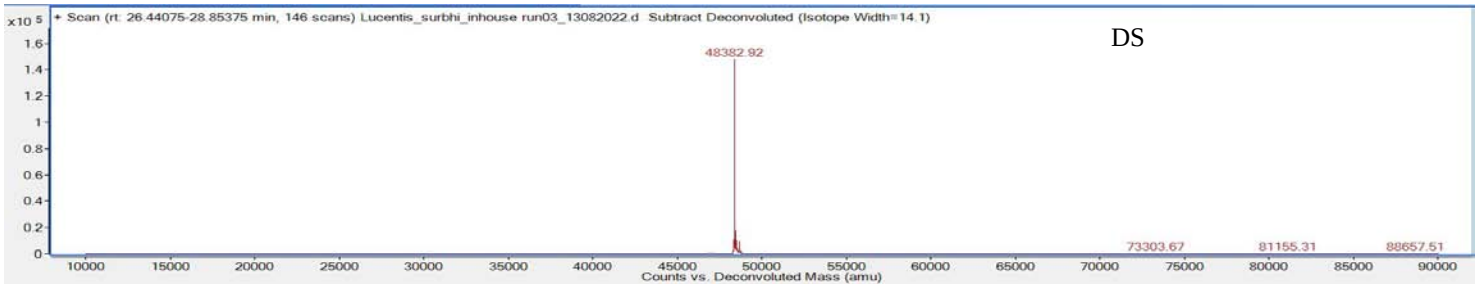
- Novel refolding process: Refolding yield of **30-35% vs the industry standard of 15%.**
- Novel continuous processing platform: Results in **reduction in cost of manufacturing** by 80% for clinical and 75% for commercial production.

Relevant publications:

- Integrated continuous processing of proteins expressed as inclusion bodies: GCSF as a case study, *Biotechnology progress* (2017) 33 (4), 998-1009
- Economic assessment of continuous processing for manufacturing of biotherapeutics, *Biotechnology Progress* (2021) 37 (2), e3108

Selected Data
Biosimilarity - Intact mass analysis

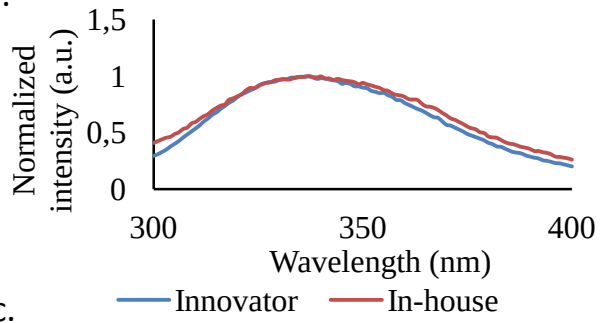




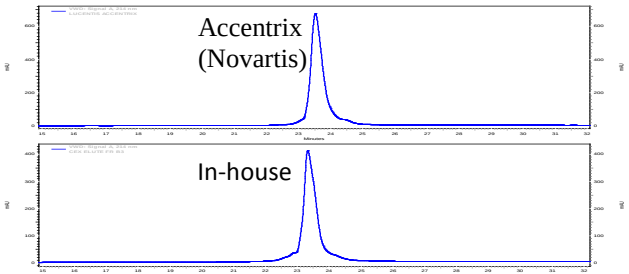
The Total Ion Chromatogram (TIC) represents the deconvoluted spectra in comparison of intact analysis between innovator and drug substance (DS). **Confirms the correct molecular mass of Ranibizumab.**

Selected Data
Biosimilarity - Peptide mapping fingerprinting

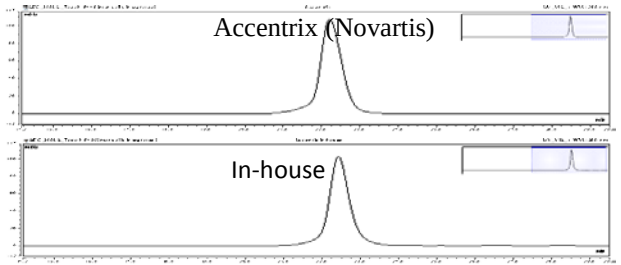
a.



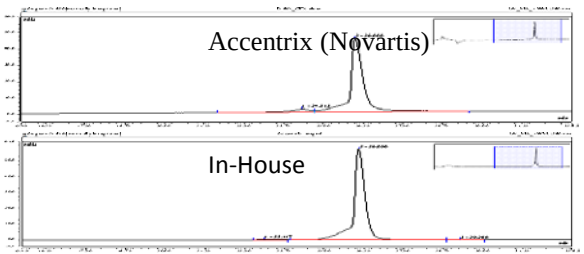
b.



c.



d.



Percentage of variants of innovator vs DS

Sample	Acidic	Main	Basic
Accentrix (Novartis)	0.12	99.8	0.08
In-house	2.35	97.65	0

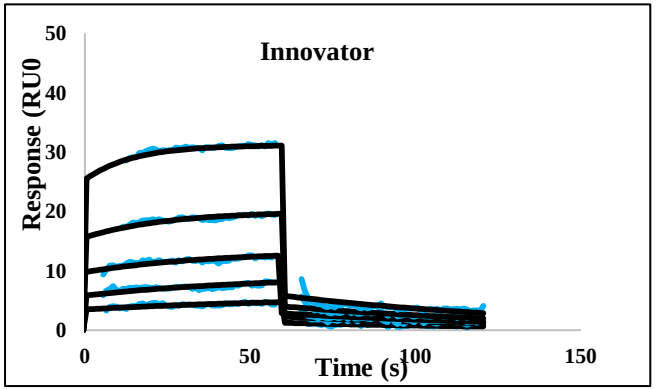
Confirms a) **Identical tertiary structure** (fluorescence spectra), b) **Similar purity** (RP HPLC ~ 99%), c) **Similar aggregation** (purity ~ 99%), d) **Similar charge variant profile**

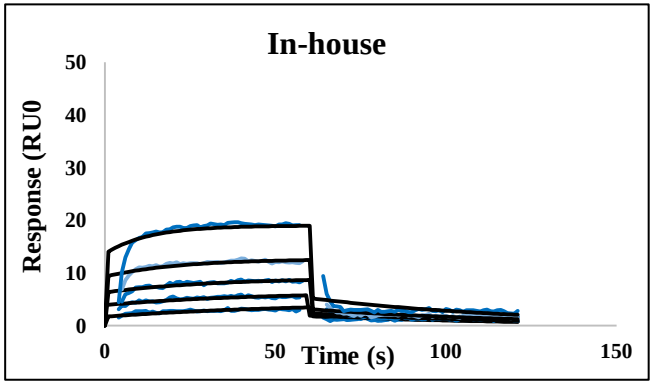
Selected Data
Biosimilarity – Functional characterization

Binding kinetics (SPR) of DS of Lucentis and Accentrix (Novartis)

Name of the Sample	ka	kd	KD (M)	Binding activity
Accentrix (Novartis)	4.28E-08	1.33E-07	1.01E-08	No difference
DS	2.19E-08	1.76E-07	1.27E-08	

Confirms similar binding activity





Summary of Biosimilarity analysis vs. Accentrix (Novartis)

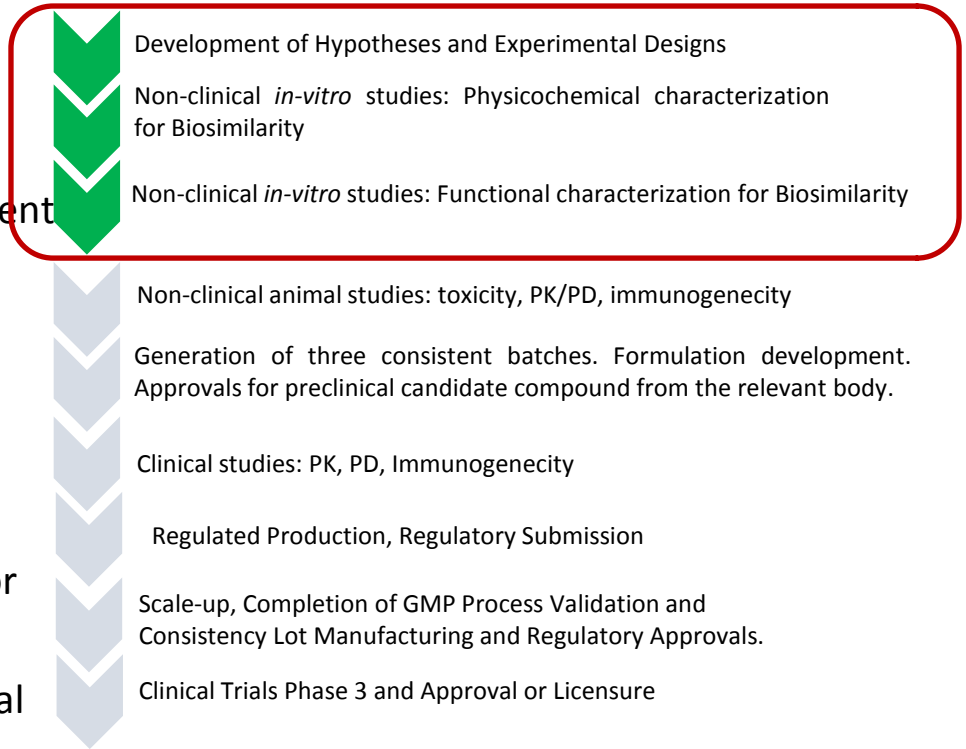
	CQA	Characterization	Status
Physiochemical characterization	Purity	RP-HPLC	Similar profile to Innovator
	Size heterogenity	SEC	~ 99% purity
	Charge variant	CEX	Acidic : 2.35, Main : 97.65
	Intact mass analysis	LC-MS	Identical profile
	Reduced mass analysis	LC-MS	Pending
	Amino acid Sequence (Primary sequence)	Peptide Mapping by Mass Spectrometry	Pending
	Disulfide linkage	LC-MS	Pending
	Secondary/ tertiary structure analysis	CD/Fluorescence spectroscopy	CD - Pending/Tertiary structure identical to Innovator
Functional characterization	Binding kinetics	SPR	Similar binding affinity compared to innovator
	HUVEC anti-proliferation assay	Cell-based assay	Pending

Current Status of Technology and Path Ahead

Clone: Purchased from Thermo Scientific

Stage of Development

- Upstream and downstream process development complete
- Process has been demonstrated up to 5L bioreactor
- Titer of **0.2 g/L in 5 L bioreactor**
- Purification yield of 23 ± 2 %
- Analytical and functional similarity to innovator molecule has been established
- **Cost of manufacturing** lower by 80% for clinical and 75% for commercial production



Next steps - Interest in Technologies

CBT team has demonstrated capabilities in **clone development, upstream and downstream processing, formulation.** The next step would be:

- Collaborate with companies interested in licensing and taking the biosimilars to the market
- Co-development of other biosimilars

Seeking Industrial partners interested in:

- Licensing technology knowhow with patents
- Sponsoring further technology advancement and scale-up
- Utilizing the R&D skills for other projects
- Collaborative development/ bidding for joint projects
- Licensing of patents

Dr Anurag Rathore's Group

Center of Excellence
Biopharmaceutical Technology

Lead Scientist: Prof Anurag Rathore

EXPERIENCE

Academic:
- **Current affiliations : Coordinator**, DBT CBT, **Professor,** Deptt of Chem Engg, **Dean,** Corporate Relations at IITD
- **Past affiliations**: UCLA, Washington Univ, & Yale University

Past Industry affiliations: Amgen Inc. & Pfizer Biologics

Expertise: Continuous processing, Stability of biotech therapeutics, Analytical and functional characterization of biosimilars, Scientific and regulatory issues of biosimilars

Agilent Thought Leader Award 2020

Fact file of Prof Rathore's Lab:

- **Authored more than 700** publications in his areas of expertise.
- Current Team strength:
  - 20 PhD students
  - 20 Post-doctoral
  - 10+ SRF/JRF
- **13 unique patent families** (Filed internationally)
- State-of-the-art **bioprocess development till 10 L scale, analytical and functional characterization facilities**

Partners: Tech transfer, Collaborations and Consultancy projects

FDA, CDSCO, NIST National Institute of Standards and Technology, TATA CONSULTANCY SERVICES, ABB, Ansys, Agilent Technologies, J&J, Biocon, Waters, Department of Biotechnology Government of India, GE, SANOFI, SUN PHARMA, APPLIED MATERIALS, DSM, PALL, ThermoFisher SCIENTIFIC, Dr.Reddy's, sartorius stedim Biotech

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Tech Transfer Hub

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