

Ranibizumab, Anakinra & Others

Technology from the group of Rahul Bhambure
at **CSIR-National Chemical Laboratory, Pune, India**

Match Maker/ Biosimilars / 31 Aug 2021/DrBhambure_CSIR-NCL

Outline

- ◆ About **CSIR National Chemical Laboratory**
- ◆ About **Bioprocess Engineering Group**
- ◆ Technology 1: Ranibizumab
- ◆ Technology 2: Anakinra
- ◆ Other Capabilities and Offerings
- ◆ The Next Steps

About CSIR-National Chemical Laboratory



- ◆ The National Chemical Laboratory is a constituent lab of the Council of Scientific and Industrial Research, India located in Pune, India with a focus on chemical, materials and biological sciences and engineering
- ◆ **NCL holds a track record of technology transfer (>200 technologies transferred) and working with industry (including many Fortune 500 and Sensex 50 companies);** offers attractive models of engagement and flexible terms for IP. It is a **publicly funded** non-profit R&D lab & **DSIR recognized SIRO** (R&D project sponsors can claim tax benefits; Eligible for CSR support)
- ◆ **NCL holds a long list of meritorious partnerships with industry clients** which range from short term to long term engagements. (<https://www.ncl-india.org/files/PartnershipWithIndustry/MajorCustomers.aspx>)

Bioprocess Engineering Group



Dr Rahul Bhambure

Senior Scientist
Chemical Engineering and Process
Development Division,
CSIR-NCL, Pune, India

Recognitions:

DST Early Career Research Award

Past affiliations:

University of Delaware, IIT Delhi, ICT
Mumbai

Expertise:

Biochemical engineering; Bioprocess development;
Biopharmaceutical manufacturing (upstream and downstream);
Applied protein biophysics

Fact file of Dr Bhambure's Lab:

- More than 10 years of experience in the field of biosimilars
- Current team strength: 6
- Well equipped labs and analytical facilities including continuous processing platform for monoclonal antibody therapeutics, high resolution and high definition mass spectrometer



Focus of Industry engagement of the Bioprocess Engineering Group

Industry interaction for projects and technology transfer



An unique initiative to provide solutions for various **process and product related challenges** in various **recombinant protein manufacturing**

- ◆ Joint **process development** projects with industry to provide de-risked **intellectual property** based processes
- ◆ Collaborative project for **structural and functional characterization** of various recombinant proteins
- ◆ **Consultative services** for bioprocess optimization & analytics
- ◆ Applied **skill development** for post graduates and industry resources

Bioprocess Engineering Laboratory at NCL: Infrastructure and facilities

Upstream

- **BioLector® microfermentation system**
- **Bioreactor (New Brunswick: capacity up to 10 liters)**
- Biorad C1000 PCR
- Biosafety cabinets
- Shakers
- Cell homogenizer (Microfluidics corporation)
- -20 freezer; -80 freezer
- Water purification system (Type III, II and I, Cascada system, Pall)

Formulation

- **Optimax and FBRM for crystallization**
- CHRIST Lyophilizer
- SprayMate spray drier

Downstream

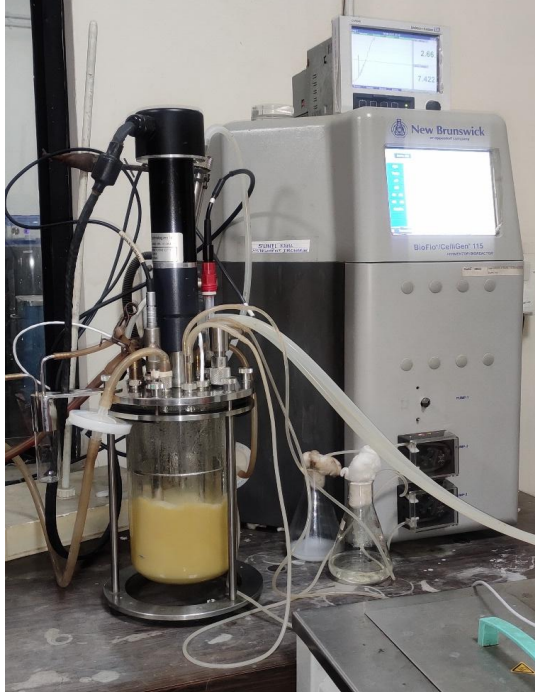
- **AKTA purifier**
- **AKTA Avant**
- **AKTA pure**
- **Twin column SMB system for continuous purification of therapeutic proteins**
- **Conventional SMB system**
- **TFF system for UF/DF**
- **Hollow fiber membrane modules for micro/ultra/nano filtration**
- Eppendorf lab scale refrigerated centrifuge
- Radial flow chromatography columns
- Axial flow chromatography columns of variable capacities
- Cold cabinet
- pH and conductivity meter (Mettler Toledo)

Analytical Characterization

- **HPLC (Agilent 1260 and Agilent 1200) with RI, PDA and FL detector**
- **Waters ACQUITY UPLC I-Class System with PDA and FL detectors**
- UV-visible dual beam spectrophotometer (Shimadzu and Chemito)
- Circular Dichroism (CD) spectrometers (Jasco Inc)
- Fluorescence spectrometer (Jasco Inc)
- FTIR spectrometer (Jasco Inc)
- NanoDSF spectrometer
- Biorad electrophoresis and western blot system
- Thermo scientific microplate UV-visible reader
- Biacore T200

Glimpses of Select Facilities and Equipment at Bioprocess Engg Group

Upstream



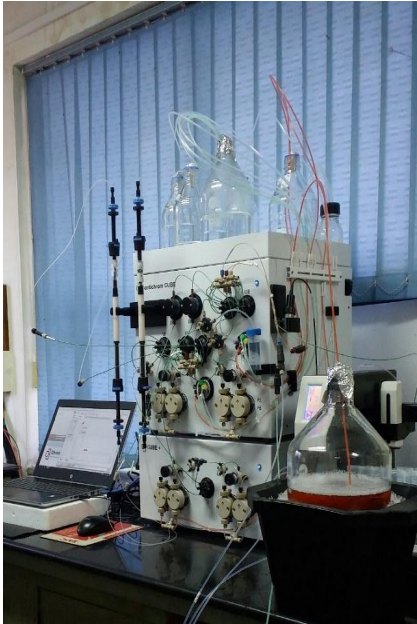
Bioreactor up to 10 liter capacity



BioLector® microfermentation system

Glimpses of Select Facilities and Equipment at Bioprocess Engg Group

Downstream



Twin column continuous chromatography



AKTA pure



Glimpses of Select Facilities and Equipment at Bioprocess Engg Group

Analytical Characterization



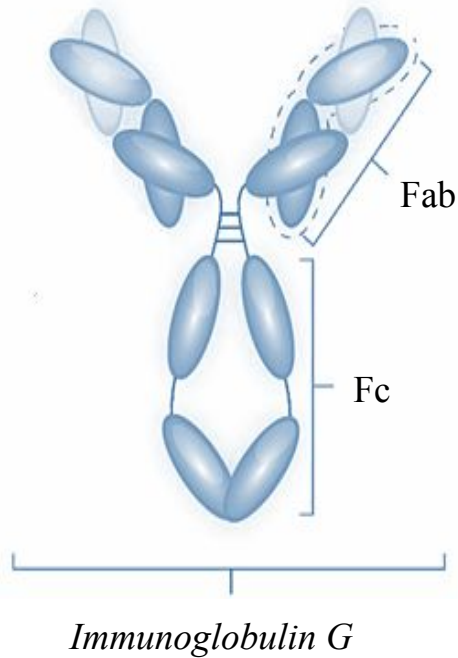
Mass Spectrometer



HPLC systems

Technology 1: Ranibizumab

Primer: Antibody fragments



- Fab is the multi-domain protein containing:
 - **heavy chain** composed of a variable (VH) and the first constant (CH1) domains
 - **light chain** composed of the light variable domain (VL) and the constant domain (CL)
- Eight Fab molecules approved by the US Food and Drug Administration
 - six of which are produced using **E. coli host cell**, which include rHu Ranibizumab, rHu Certolizumab pegol, Blinatumomab, Moxetumomab pasudotox, rHu Caplacizumab, and rHu Brolucizumab
 - Two other antibody fragment rHu Abciximab and rHu Idarucizumab are produced using **mammalian host cell**

Primer: Why antibody fragments?

Advantages

- Easy penetration in tissues
- Elimination of the immunogenicity due to lack of Fc region
- ***Bacterial expression of antibody fragments offers time and cost-effective high throughput manufacturing processes as compared to monoclonal antibody production using mammalian cell systems***

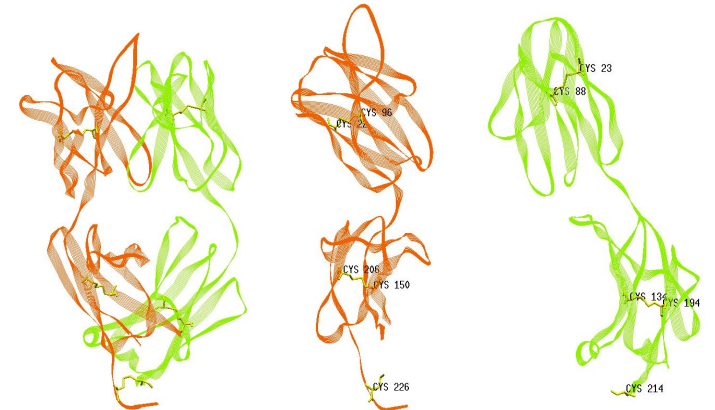
Disadvantages

- Reduced stability of the fragments compared to full-length antibodies
- Short circulation half-life
- Requirement of an efficient in-vitro refolding process

About Ranibizumab

Ranibizumab is a **recombinant humanized IgG1** monoclonal antibody fragment 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)**, Neovascular AMD (most severe vision loss), Macular edema following retinal vein occlusion (RVO), Diabetic macular edema (DME), Diabetic retinopathy (DR) and Myopic choroidal neovascularization (mCNV)



Fab

(48.38 kDa)

Heavy chain

(231-residue
heavy chain of
24.95 kDa)

Light chain

(214-residue
light chain of
23.43 kDa)

Note: Total five disulfide bond comprises two intra disulfide in each chain with one inter disulfide between light and heavy chain

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
<ul style="list-style-type: none">• Razumab: 2.3mg Injection @ ~ \$ 270• Lucentis: 0.5 mg injection @ ~\$ 1120	<ul style="list-style-type: none">• 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

- Clone, upstream and downstream process
- UPSTREAM: Single fermentation batch required: Antibody fragment expression using duet vector system.
High throughput refolding process : refolding yield of 40-45 %
- DOWNSTREAM: Purification process of recombinant AbF from inclusion bodies
 - Novel multimodal chromatographic purification steps > 2X improvement in productivity
 - Purification platform applicable to: in-vitro refolded and soluble expressed antibody fragments
 - Overcomes requirement for affinity chromatography, a cost center; uses anion and cation exchange, reducing cost by 1/3rd

Related Patents:

A Method For Producing Refolded Recombinant Humanized Ranibizumab

Priority date: 19.05.2017; [WO2018211529](#) - IN, CN, KR, EP, JP, BR, CA, US, MX, US

A Process For The Purification Of Recombinant Antibody Fragments

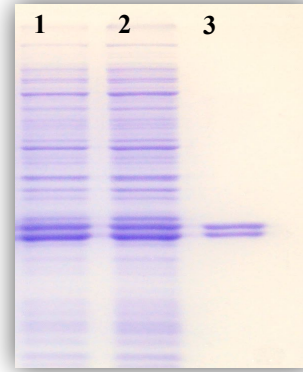
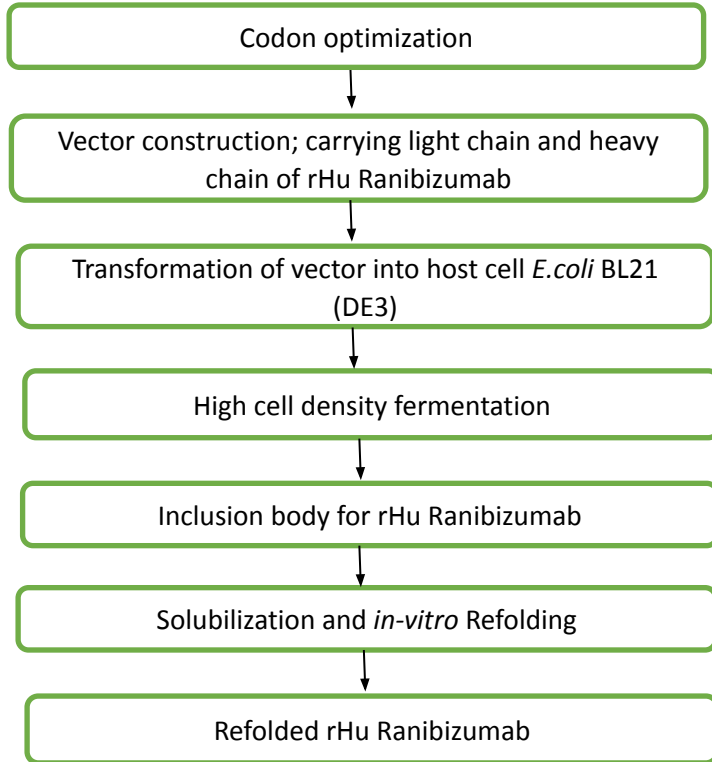
Priority date: 24.03.2017; [WO2018173075](#) - IN, KR, CN, EP, US, JP, BR, CA, MX

Relevant Publication:

[K. Gani, R. Bhambure, P. Deulgaonkar, D. Mehta, M. Kamble, Understanding unfolding and refolding of the antibody fragment \(Fab\). I. In-vitro study, Biochemical Engineering Journal. 164 \(2020\) 107764.](#)

Selected Data- Clone and upstream details

Upstream



Expression scale: 1 liter bioreactor

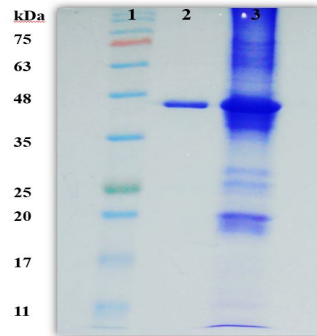
Lane 1: NCL-rHu Ranibizumab (Reducing SDS-PAGE showing expressed light and heavy chain)

Lane 2: NCL-rHu Ranibizumab replicate batch

Lane 3: Innovator rHu Ranibizumab (Lucentis)



***In-vitro* dilution based refolding**



***In-vitro* refolding scale: 2 liter reactor**

Lane 1: Molecular weight marker

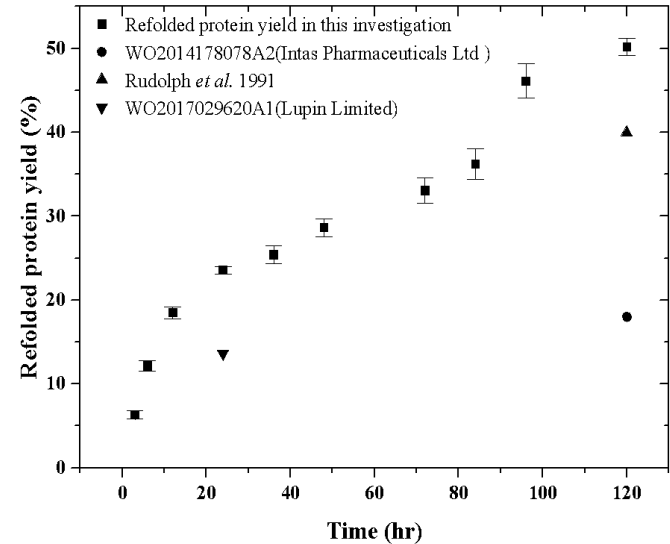
Lane 2: Innovator rHu Ranibizumab (Lucentis)

Lane 3: NCL refolded rHu Ranibizumab (Non-reducing SDS-PAGE)

In-vitro refolding: rate limiting step in antibody fragment manufacturing

Refolding

- Dilution based refolding is the only scalable alternative for large scale production of antibody fragments
- *In-vitro* refolding process is the key rate limiting step in overall manufacturing of antibody fragments
- Reported *in-vitro* refolding yield for antibody fragments:
 - Intas: **9.0 refolding yield in 120 hour**
 - Lupin: **15.0 % refolding yield in 72 hour**
 - Rudolph *et al.* : **40.0 % refolding yield in 120 hour**

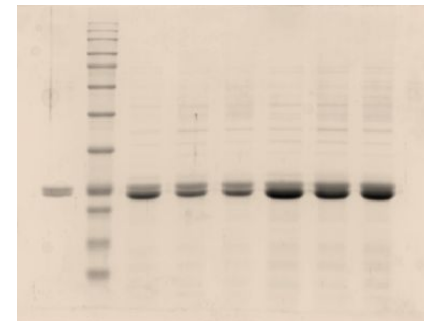
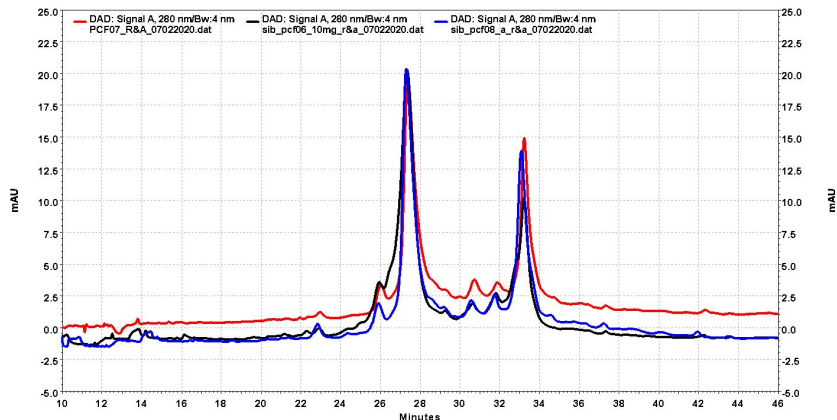


References:

- J. Buchner, R. Rudolph, Renaturation, purification and characterization of recombinant fab-fragments produced in Escherichia coli, Nat. Biotechnol. 9 (1991) 157–162
- H. Shandilya, H. Gadgile, V. Farkade, Cloning, expression & purification method for the preparation of Ranibizumab, US20160289314A1 (2016).
- S. Somani, A. Pandey, A. Nishra, R. Mody, An improved refolding process for antibody's fragments, WO2017029620A1 (2017).

Upstream batch consistency for IB production of rHu Ranibizumab

Upstream



Lane 1	Standard (4µl)
Lane 2	Molecular weight marker
Lane 3	PC01_IB (4µl)
Lane 4	PC02_IB (4µl)
Lane 5	PC03_IB (4µl)
Lane 6	PC01_IB (7µl)
Lane 7	PC02_IB (7µl)
Lane 8	PC03_IB (7µl)

Batch fermentation	Protein (mg/L) Batch PC01	Protein (mg/L) Batch PC02	Protein (mg/L) Batch PC03
IBs per litre of media	8806.00	8575.00	8755.00
Light chain	1022.63 ± 71.97	955.08 ± 7.34	948.62 ± 18.38
Heavy chain	402.80 ± 46.97	419.29 ± 3.39	454.08 ± 8.95
Total protein	1425.44	1374.37	1402.70

Downstream platform for rHu Ranibizumab

Downstream

Refolded rHu Ranibizumab

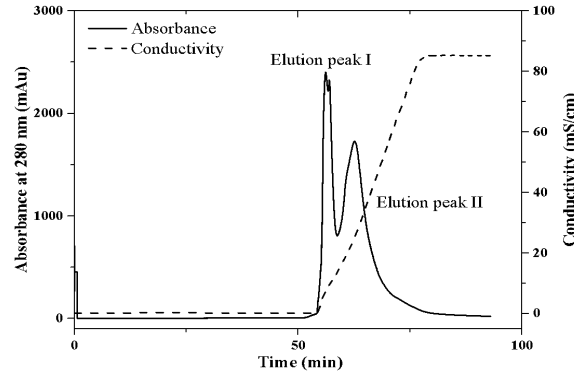
Ultrafiltration and Diafiltration

Multimodal chromatography I

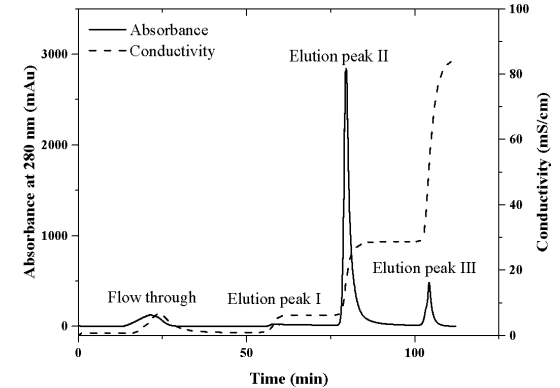
Multimodal chromatography II

Ultrafiltration and Diafiltration

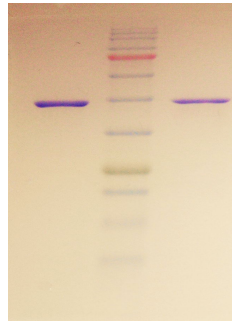
Purified rHu Ranibizumab



Multimodal chromatography I



Multimodal chromatography II



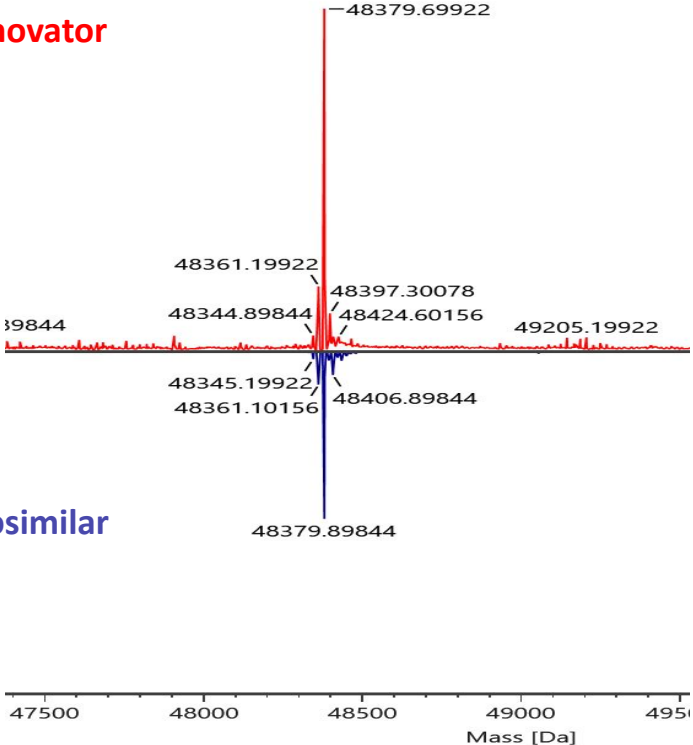
Lane 1: Purified NCL-rHu Ranibizumab
Lane 2: Molecular weight marker
Lane 3: Innovator-Ranibizumab

Conclusion: Designed a novel multimodal chromatography based purification platform for rHu Ranibizumab downstream processing

Biosimilarity data: Intact mass data analysis

Analytical

Innovator

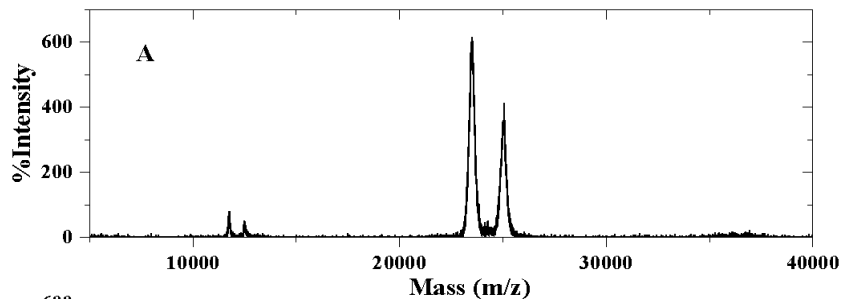


Sample	Intact Mass (Da)
Lucentis®	48379.713 ± 0.038
Biosimilar	48379.719 ± 0.023

Biosimilar

Biosimilarity data: MALDI-TOF Analysis

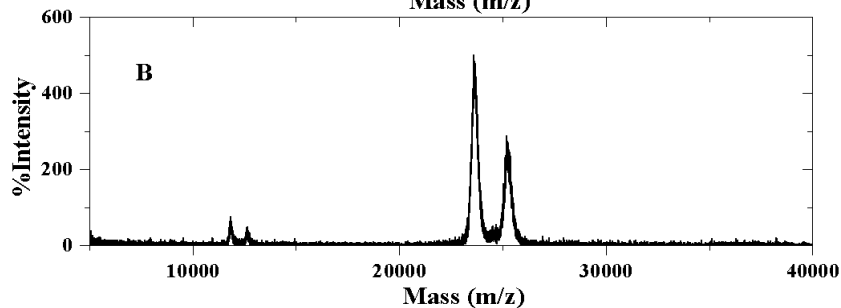
Analytical



MALDI-TOF analysis for reduced Ranibizumab molecule

A: Innovator rHu Ranibizumab

B: NCL rHu Ranibizumab



Protein name	Chain Name	Observed mass (Da)
Lucentis®	Light Chain	23428.596±0.002
Lucentis®	Heavy Chain	24952.579±0.013
Biosimilar rHu Ranibizumab	Light Chain	23428.773±0.014
Biosimilar rHu Ranibizumab	Heavy Chain	24952.565±0.010

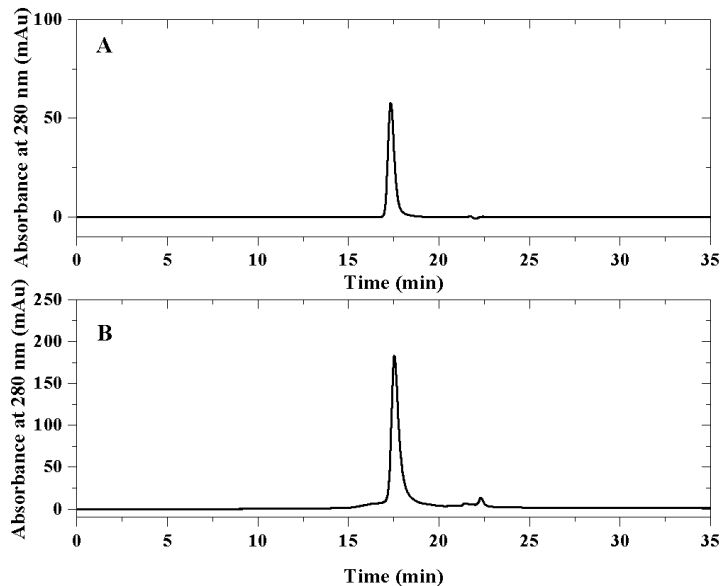
MALDI-TOF analysis for reduced Ranibizumab molecule

A: Innovator rHu Ranibizumab

B: NCL rHu Ranibizumab

Biosimilarity data: RP-HPLC and SEC-HPLC

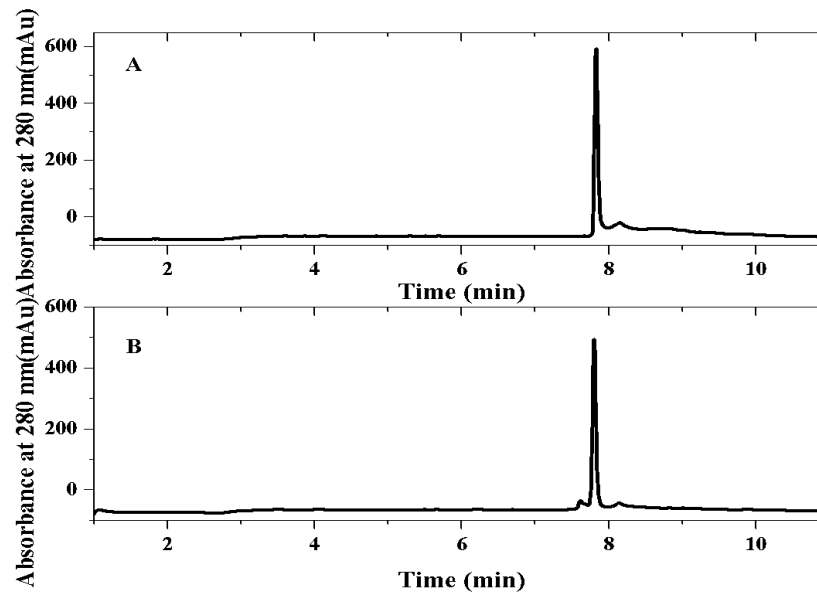
Analytical



Size exclusion chromatogram of purified rHu Ranibizumab

A: Novartis rHu Ranibizumab

B: Refolded rHu Ranibizumab

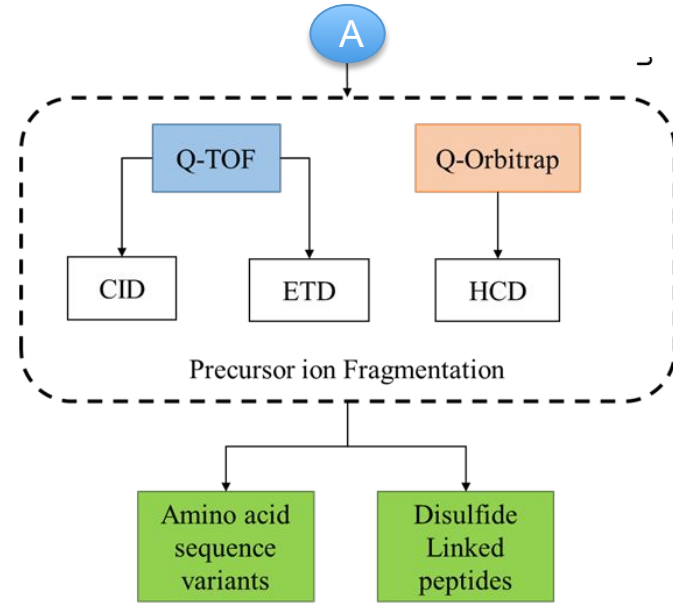
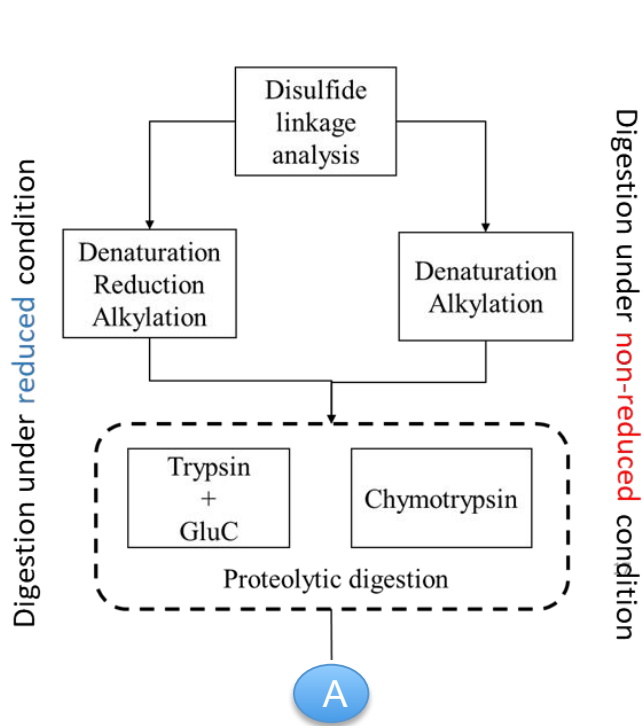


Reversed phase HPLC chromatogram of purified rHu Ranibizumab.

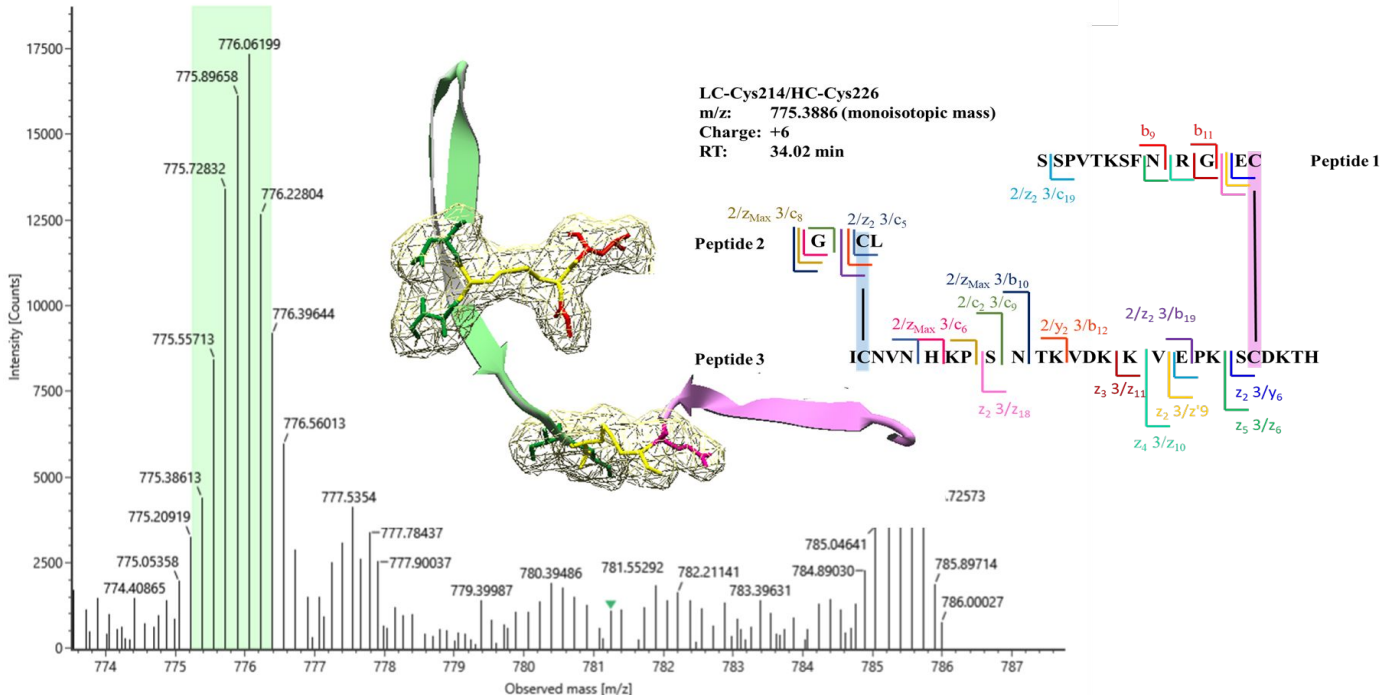
A: Novartis rHu Ranibizumab

B: Refolded rHu Ranibizumab.

Mapping intra and inter-chain disulfide bonds



Inter-chain disulfide bond: LC-Cys214-HC-Cys226



Summary of Biosimilarity Analysis

Test	Test performed at CSIR-NCL
Molecular weight	SDS- PAGE, MALDI-TOF, SEC, ESI-MS/MS
Secondary structure	CD Spectroscopy & Fluorescence Spectroscopy
Carbohydrate content and details of component	Not applicable for this molecule
Aggregate quantification	MALDI-TOF and SEC analysis
HCP quantification	ELISA based assay < 100 ppm in DS
Residual DNA	Picogreen assay < 10 ng/dose in DS
Amino acid sequence	LC-MS/MS
Disulfide bond mapping	LC-MS/MS
Pyrogenic testing	Not applicable for work at CSIR-NCL

- Completed all the biosimilarity analysis required for RCGM submission
- Good agreement between an innovator and developed biosimilar protein

Current Status of Technology

Stage of Development

- Protein expressed at 10 L scale reactor
- Completed five consistency batches at 10 liter scale

Key process parameters

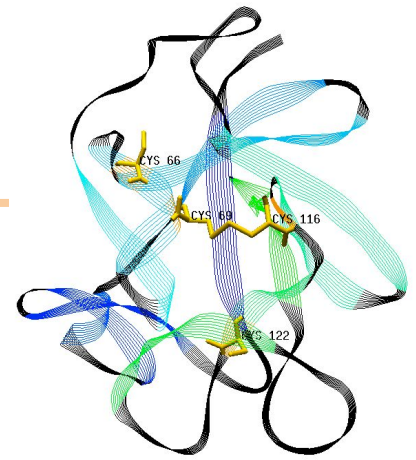
- Achieved yield of **2.81 ± 0.10 g/L**



Technology 2: Anakinra

About Anakinra

Anakinra is a **recombinant, nonglycosylated form** of the **human interleukin-1 receptor antagonist (IL-1Ra)**, that can reduce the activity of interleukin-1, a key driver of inflammation in autoimmune and autoinflammatory diseases.



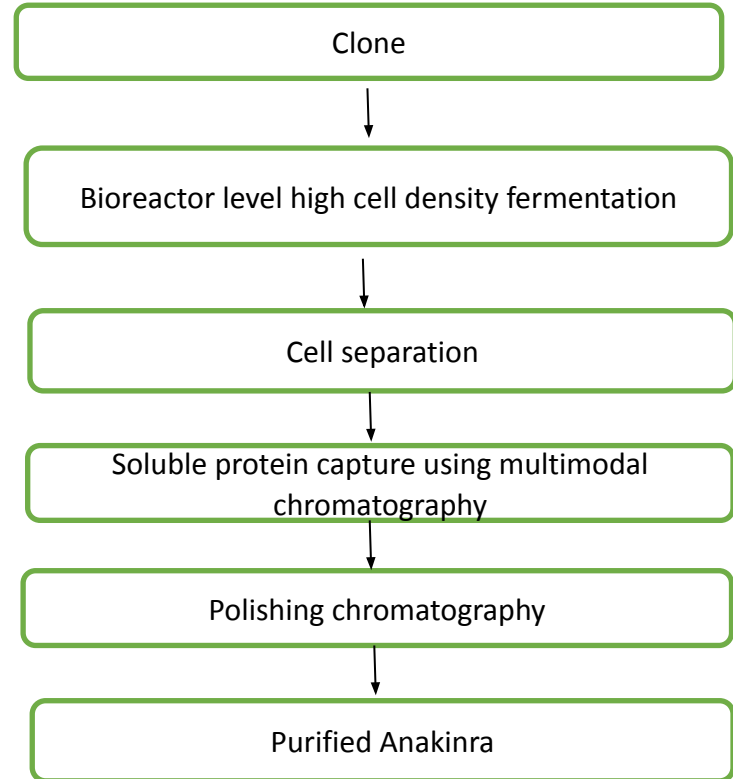
- **Originator / reference product:** **Kineret** is marketed by Swedish Orphan Biovitrum, approved by the USFDA in 2001 and by EMA in 2002. The **original patent on Anakinra expired in 2008.**
- **Indications:** Used in rheumatoid arthritis as a **second in line treatment** to a Disease Modifying Anti Rheumatic Drug (**DMARD**), **Stills disease** (a rare form of rheumatoid conditions), **Neonatal-onset multi-system inflammatory disease**, Cryopyrin-associated periodic syndromes (CAPS), Familial Mediterranean fever, another inherited periodic fever syndrome

The Opportunity: Why you should be interested?

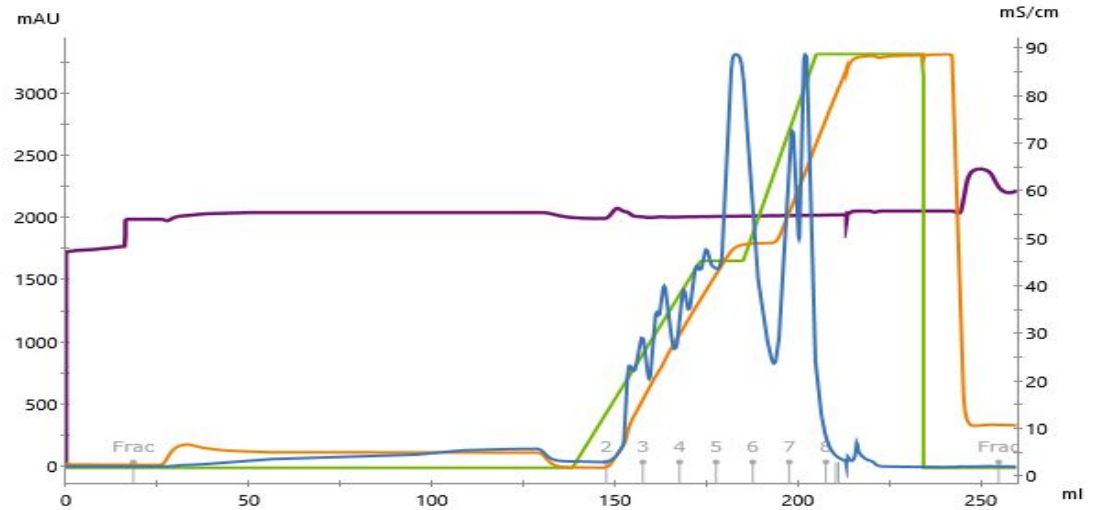
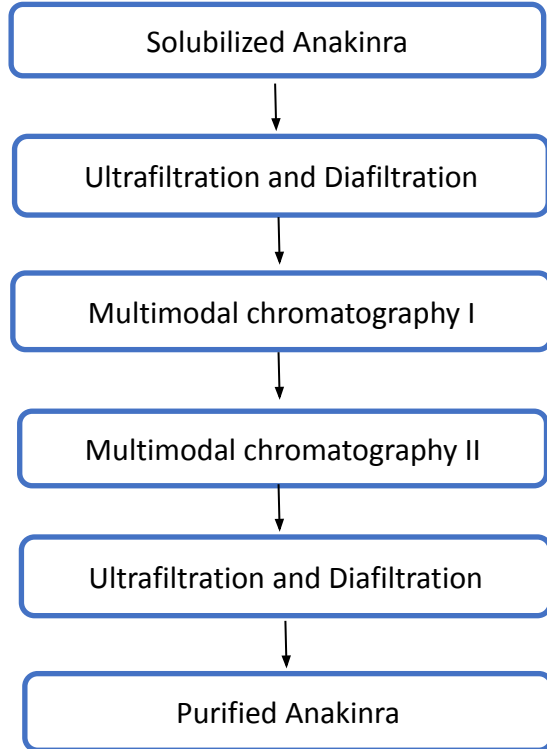
- **Market interesting:**
 - Nearly **4% of the world's population** is affected by one of more than 80 different autoimmune diseases, **rheumatoid arthritis** being one of the **most common**. (Source: [NSCF](#))
 - **Global prevalence** of rheumatoid arthritis is between **0.24-1%**, varies considerably around the globe (Source: [NCBI](#))
 - Cost of manufacturing Anakinra (a 2nd in line drug for RA) is 1/10th that of Rituximab.
- **New indications/ application:**
 - Originator company SOBI state that the interest in Kineret remains strong with more utility being tested out
 - As a treatment for COVID-19-induced SARS (severe acute respiratory syndrome) and CSS (cytokine storm syndrome) was featured in prestigious publications such as **The Lancet Rheumatology**. EMA has started **review** of Anakinra for **treatment of COVID 19 in adult** patients as on July 2021.
 - Expanded scope with studies underway: **Familial Mediterranean fever, Deficiency of interleukin-1 receptor antagonist (DIRA), Moderate to severe COVID treatment, Psoriasis**
- **Industry not yet crowded:** Very few companies seem to be working on developing biosimilars of the molecule.
- **Cost still high:** \$ 1194 (for 4.69 ml) and \$ 3811 (for 18.76ml)
- **Opportunities for process innovations to reduce costs**

The Technology Offering

- Clone, upstream and downstream process for producing biosimilar Anakinra
- Soluble expression of Anakinra eliminating in-vitro refolding step
- Purification process involving novel multimodal chromatographic purification steps > 2X improvement in productivity
- Time and cost effective expression avoiding in-vitro refolding of protein
- Soluble protein expression > 1gm/L of fermentation broth



Downstream process platform



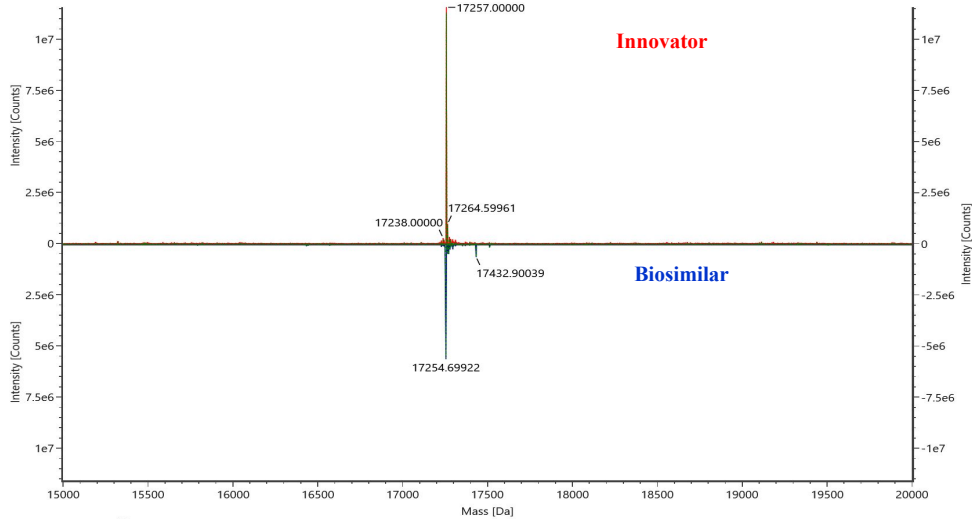
Multimodal chromatography I

Designed a novel multimodal chromatography based purification platform for Anakinra downstream processing

Biosimilarity- Intact mass analysis

Item name: 32_Kineret_IM_TuL_001

Item description: MPA, Channel name: 1: Average Time 4.0950 min : TOF MS (400-4500) ESI+ : MaxEnt1 : Combined

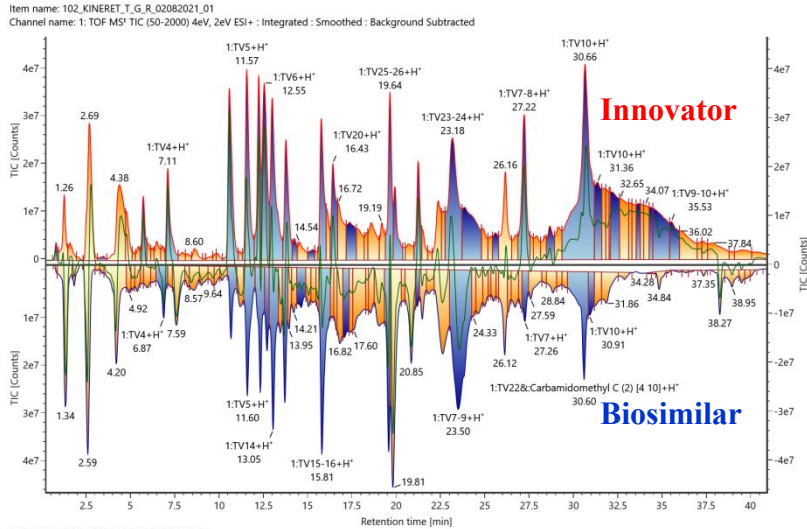


Item name: 116_Anakinra_IM_29052021_01

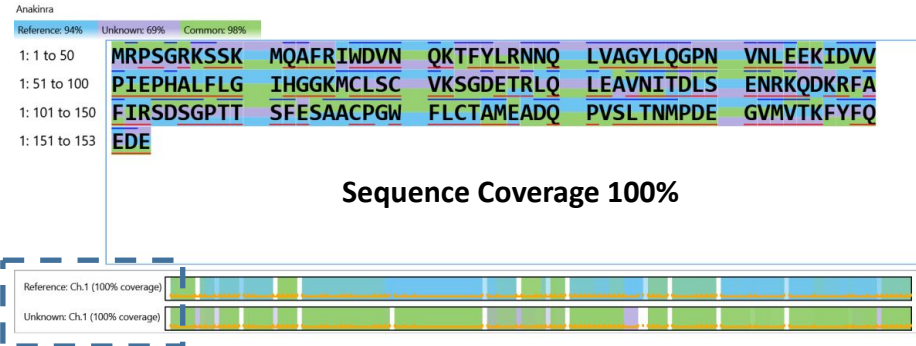
Item description: , Channel name: 1: Average Time 4.0951 min : TOF MS (400-4500) ESI+ : MaxEnt1 : Combined

Sample	Observed mass (Da)	Expected mass (Da)	Mass error (Da)
Anakinra_NCL	17254.6712	17255.4267	-0.7555
Kineret	17256.9708	17255.4267	1.5441

Biosimilarity – Peptide fingerprinting

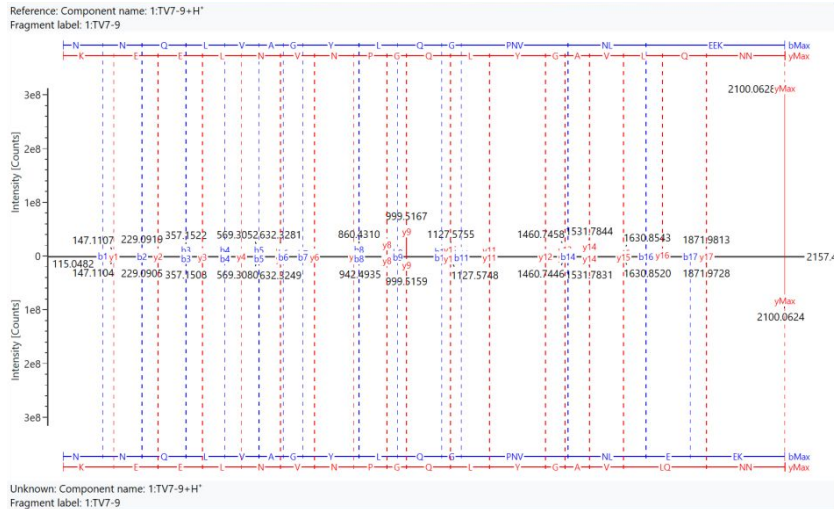


Item name: 30_Anakinra_R_T_G_11062021_01
Channel name: 1: TOF MS¹ TIC (50-2000) 4eV, 2eV ESI+ : Integrated : Smoothed : Background Subtracted



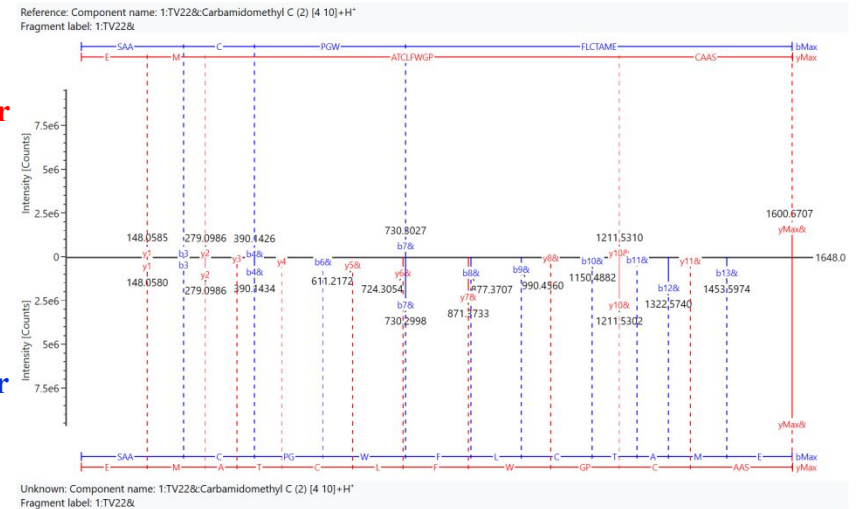
Biosimilarity – Peptide fingerprinting

Sequence confirmation at MS²



Innovator

Biosimilar



Summary of Biosimilarity Analysis

Test	Test performed at CSIR-NCL
Molecular weight	SDS- PAGE, MALDI-TOF, SEC, ESI-MS/MS
Secondary structure	CD Spectroscopy & Fluorescence Spectroscopy
Carbohydrate content and details of component	Not applicable for this molecule
Aggregate quantification	MALDI-TOF and SEC analysis
HCP quantification	ELISA based assay < 100 ppm in DS
Residual DNA	Picogreen assay < 10 ng/dose in DS
Amino acid sequence	LC-MS/MS
Disulfide bond mapping	LC-MS/MS
Pyrogenic testing	Not applicable for work at CSIR-NCL

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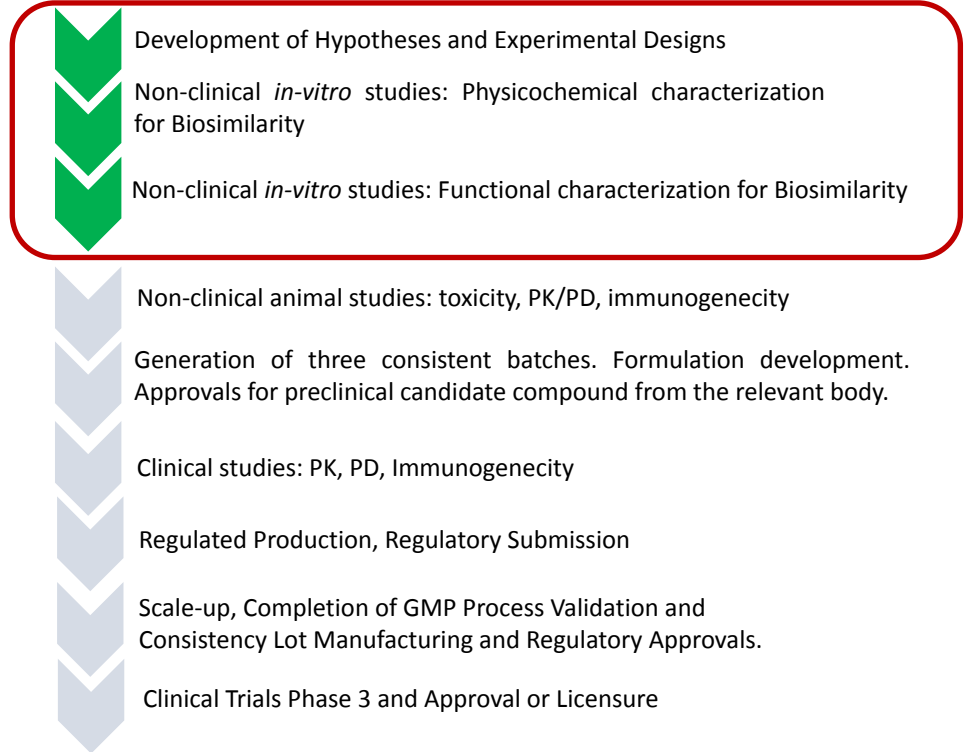
Current Status of Technology

Stage of Development

- Protein expressed at 10 L scale reactor

Key process parameters

- Yield of **Anakinra_NCL was determined to be 1.1 ± 0.20 g/L**



Other Capabilities and Offerings

Other molecules in the pipeline

Molecule	Disease indication	Stage of development
Romiplostim	Chronic idiopathic (immune) thrombocytopenic purpura (ITP)	Completed clone and upstream process development. Analytical characterization and downstream process development under progress
Teriparatide	Osteoporosis	Completed clone and upstream process development. Analytical characterization and downstream process development under progress
G-CSF	Neutropenia	Completed clone and upstream process development. Analytical characterization and downstream process development under progress
Insulin lispro	Type 1 and type 2 diabetes	Completed clone and upstream process development. Analytical characterization and downstream process development under progress
L-Asparaginase	Acute lymphoblastic leukemia (ALL)	Completed clone and upstream process development. Analytical characterization and downstream process development under progress

Next steps

Bioprocess Engg Group at CSIR-NCL is keen to forge industry partnerships for

- ◆ Advancing the biosimilar technologies presented today through *in vivo* and clinical studies.

Seeking Industrial partners interested in:

- ❖ Licensing technology knowhow with patents
- ❖ Joint development, technology advancement and scale-up projects
- ❖ Sponsored projects for process development for other biopharmaceuticals
- ❖ Industry projects utilizing expertise, capabilities and facilities with the group
- ❖ Consulting projects

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