

Adalimumab & Others

Technology from the group of Pradip Sen
at **CSIR-Institute of Microbial Technology, Chandigarh,**
India

[Match Maker/ Biosimilars / 31 Aug 2021/DrSen_CSIR-IMTech](#)

TechEx.in Case Manager:

Devanshi Patel, devanshi@venturecenter.co.in

Outline

- ◆ About **CSIR Institute of Microbial Technology**
- ◆ About **mAb based Biotherapeutics Group**
- ◆ Technology: Adalimumab (Humira)
- ◆ Other Capabilities and Offerings
- ◆ The next steps.

About CSIR-Institute of Microbial Technology



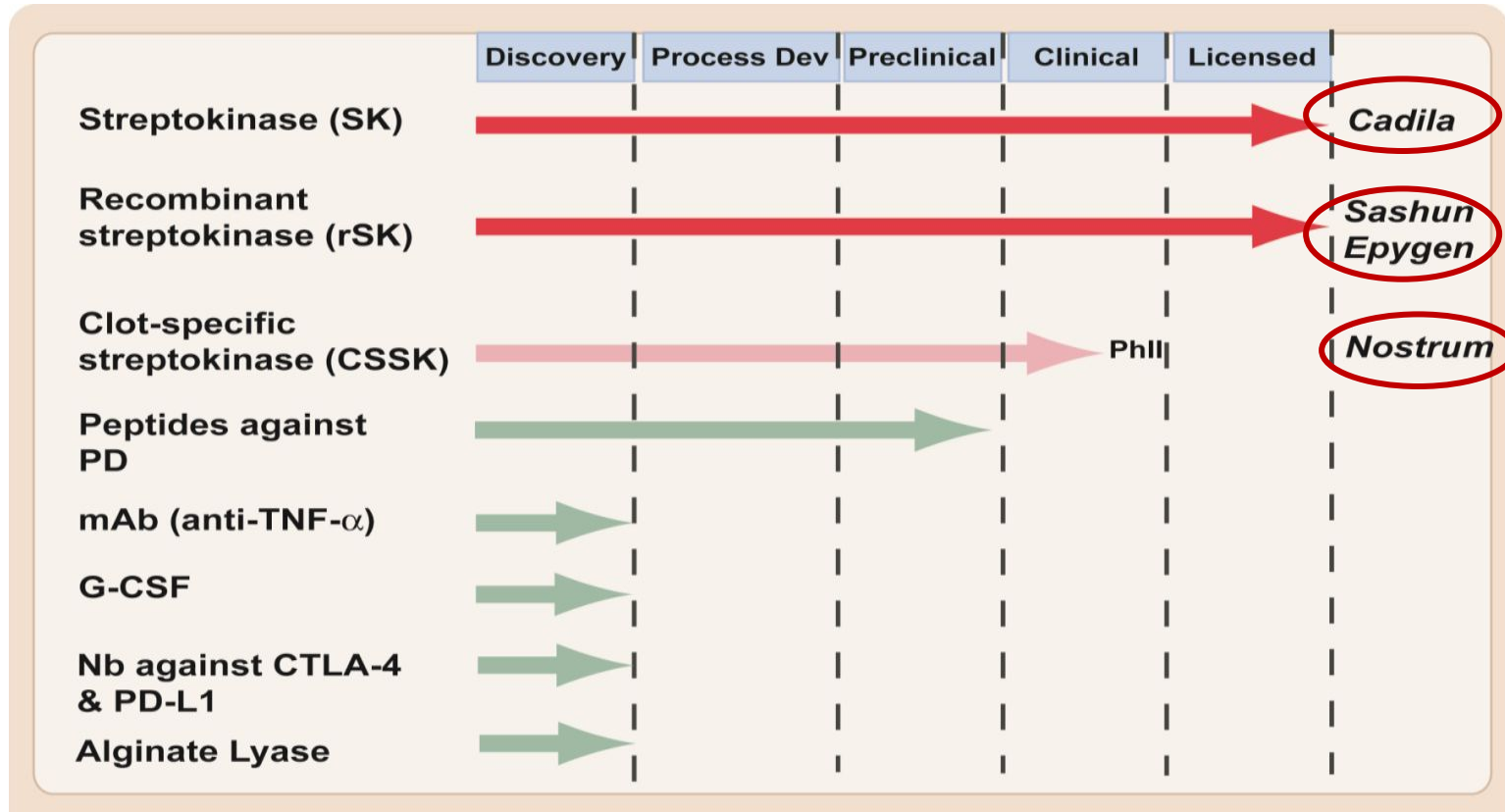
IMTech is one of the constituent labs of Council of Scientific and Industrial Research, India.

IMTech has a **track record of technology transfer** & working with industry. It successfully **commercialised Streptokinase** and its versions to **Indian (2002)** and **Clot Specific Streptokinase (CSSK) to US (2006)** companies.

The lab offers attractive models of engagement and flexible terms for IP.

A **Publicly funded non-profit R&D lab** & DSIR recognized Scientific and Industrial Research Organization (SIRO), IMTech **R&D project sponsors can claim tax benefits**. The lab is eligible for **CSR support under defined R&D areas**.

IMTech's proven track record of Biologics development



CSIR-IMTECH mAb based Biotherapeutics Group



Lead Scientist: Dr Pradip Sen

EXPERIENCE

Academic:

- **Current affiliations** : Senior Principal Scientist, monoclonal antibodies based biotherapeutics group
- **Network collaborator** - Global Challenge Research Fund project with Durham University (UK) for neglected and tropical diseases.
- **Past affiliations:** University of Northern Carolina and Humboldt University, Berlin

Expertise: Immunology, Cell biology, Biochemistry, Molecular biology, Expression of antibody construct in CHO cell line.

Fact file of IMTECH Biotherapeutics Group:

- **Dr. Pradip Sen** (lead PI) has authored more than **20 publications** in his areas of expertise.
- **Team members**
 - **Dr. Raj Kumar:** Cell and molecular biologist
 - **Dr. Beena Krishnan:** Protein Biochemist
 - **Dr. Grish Vashney:** Immunologist
- State-of-the-art **bioprocess development till 5 L scale, analytical and functional characterization facilities.**
- Group capable of performing complete **end-to-end research for select protein-based biotherapeutics** (biosimilar, biobetters and/or novel molecules)

State of the art facilities for Upstream, Downstream and Analytical to deliver Biopharma/Biologics

- **Mammalian cell fermentors** of capacities up to 5 litres (batch fermentation)
- High-capacity homogenizers, centrifugal separators, ultrafiltration, rotary vacuum filter, spray drier
- **Large-scale down stream** processing equipment



Mammalian Cell Culture Facility



Lab Scale Fermenters



Fermentation Pilot - Plant Facility (Scale: 500 L)



Technology : Adalimumab

About Adalimumab

Adalimumab is a human monoclonal antibody that **treats autoimmune diseases** by **inhibiting tumour necrosis factor** (TNF); a soluble inflammatory cytokine.

- **Originator / reference product:** The originator product, AbbVie's Humira was approved by **USFDA in Dec 2002** and **EMA in Sept 2003**. Patent will **expire in US in 2023** and **expired in Europe in June 2017**. (Source: [GabiOnline](#))
- **Indications:** **Rheumatoid arthritis (RA)**, juvenile idiopathic and psoriatic arthritis, ankylosing spondylitis, **Crohn's disease**, **psoriasis** and ulcerative colitis.

Market & Industry Overview

Market:

Market size is estimated to reach **\$4.3 Billion by 2025**, growing at a CAGR of 4.98% during the forecast period 2020-2025. Geographically, **North America** registered for **highest revenue share of 37.1%** in 2019. (Source: [Industry Arc](#))

Industry players:

- **Global:** AbbVie, Boehringer Ingelheim, Cadila Pharma (EU)
 - **Approved and ready for launch** in US in 2023*: Amgen, Novartis Sandoz, Samsung BioEpis, Pfizer, Mylan
- **Indian:** Zydus Cadila, Torrent Pharma, Reliance Lifesciences, Hetero Pharma, Glenmark Pharma

*With **AbbVie** announcing **settlement** of its **patent litigation with Boehringer Ingelheim** over Adalimumab in May 2019, **biosimilar entry** is set to **open up for US in 2023**. (Source: [Healio.com](#))

The Opportunity: Why you should be interested?

Market interesting: a) While EP patent on Adalimumab has expired, the US patent is set to expire in 2023. **Next generation Biosimilar** b) **Global prevalence** of RA is between **0.24-1%** and in **India** is **0.34%**. But for a population of 1.2 billion, it amounts to **5 million patients**, a significantly heavy burden. (Source: [Springerlink](#), [AcraaAbstracts](#)) c) **Humira** occupies an **outsized position in the biologic and biosimilar landscape**, as it netted \$16.11 billion in 2020, an increase of 8.4% over 2019.

New indications/applications: Being tested for chronic skin diseases such as eczema

Cost still high:

- Global cost between:
~\$2000-3000 per month
- India cost between:
~ \$2124 (~Rs. 1,56,000) per month (Humira)
~ \$164-328 (~Rs 15000-30000) per month (Biosimilar)

Annual Cost of treatment with Biosimilar: ~\$1966-4920 (Rs 1,44,000 - 3,60,000)

Sky-high prices

The U.S. has the highest medication prices in the world.

Country	Average monthly price: Humira
Japan	\$980
France	982
Canada	1,164
United Kingdom	1,180
Australia	1,243
Germany	1,749
United States	2,505

Sources: Bloomberg News, SSR Health, IHS Inc.

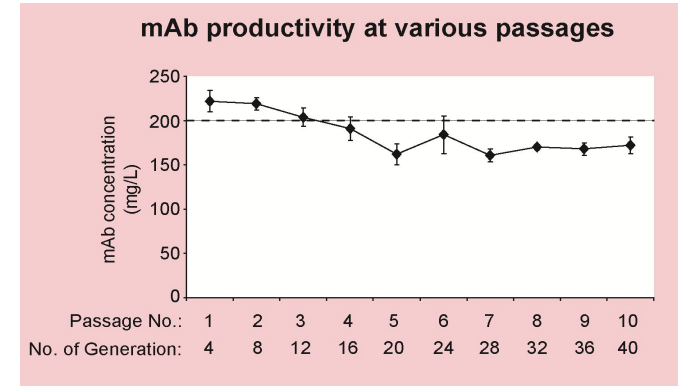
Source: [LAtimes](#)

Opportunities for process innovations to reduce costs: Higher mAb producing clone, innovation in upstream and downstream processing.

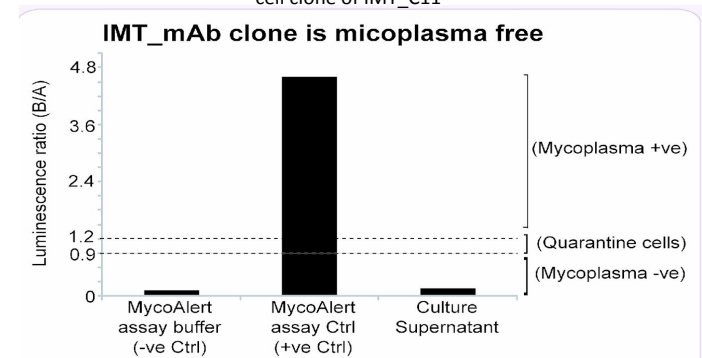
The Technology Offering

Clone Performance

- **Inhouse developed, stable, unencumbered CHO cell clone (IMT_C11)** (mycoplasma free and functional)
 - Produces : Adalimumab ~170-200 mg/L (100 ml culture vol. in 500 ml shake flask; unfed culture; repeated 3 times)
- Shows **stable mAb production through 40 generations**



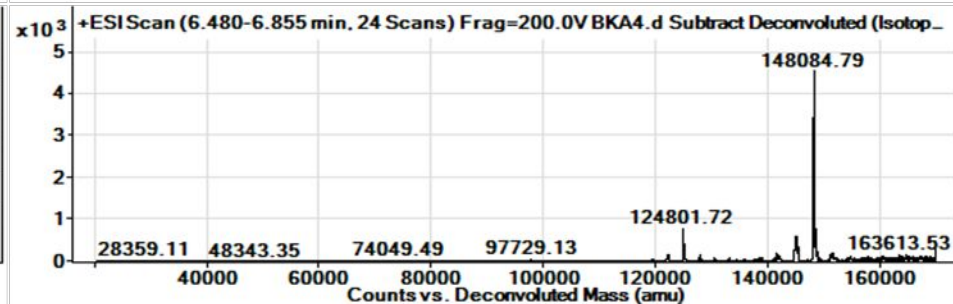
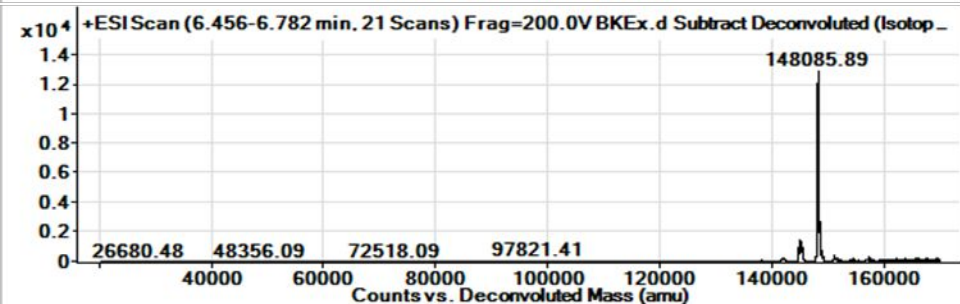
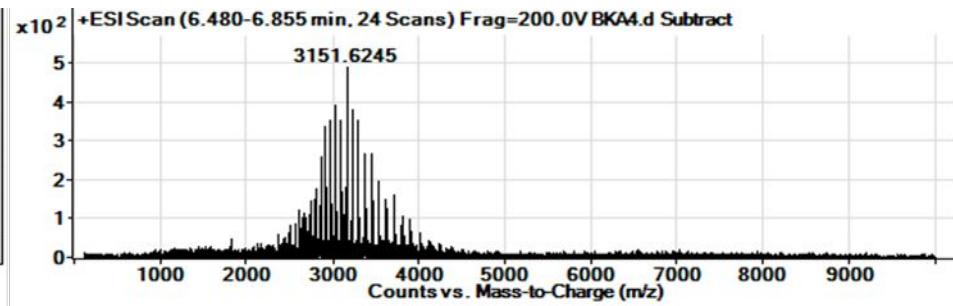
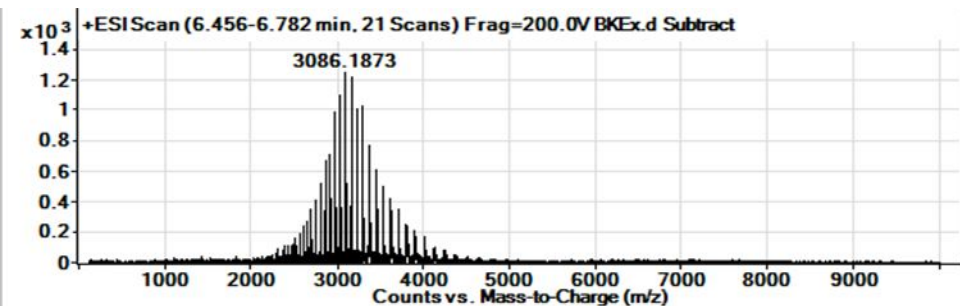
Consistent mAb production up to 10 passages observed from third round isolated single cell clone of IMT_C11



Select Data -Biosimilarity: Intact Mass Analysis

Exemptia

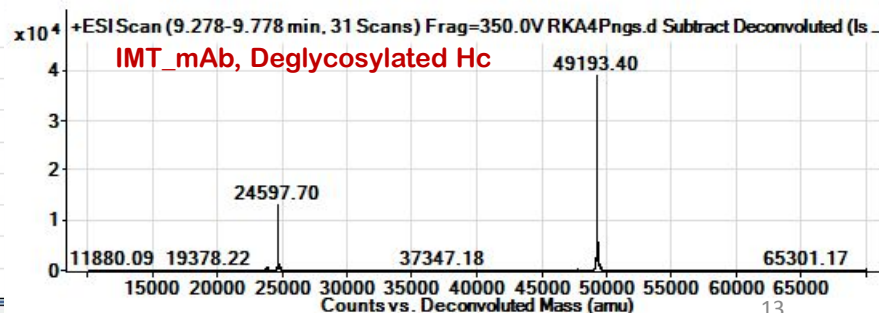
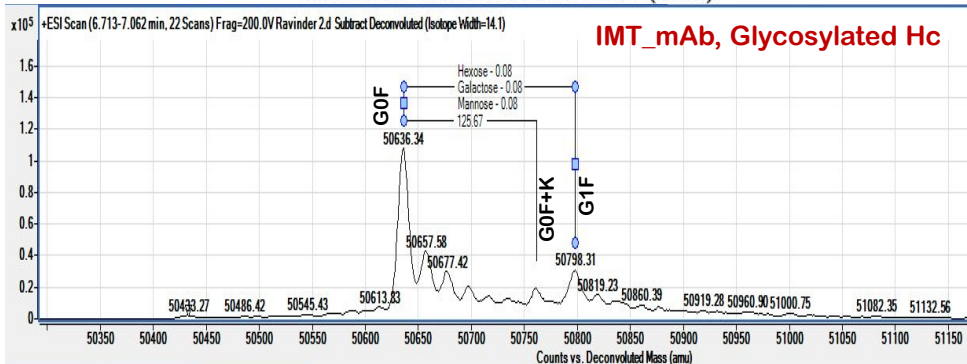
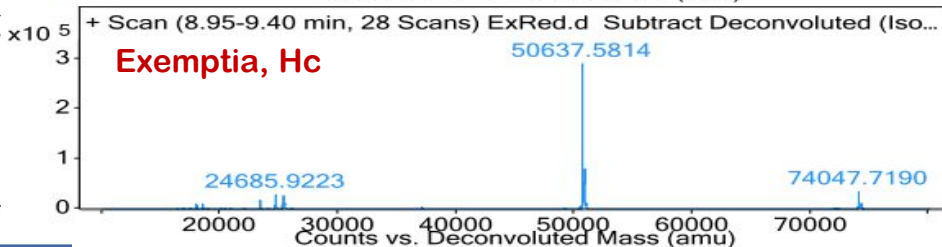
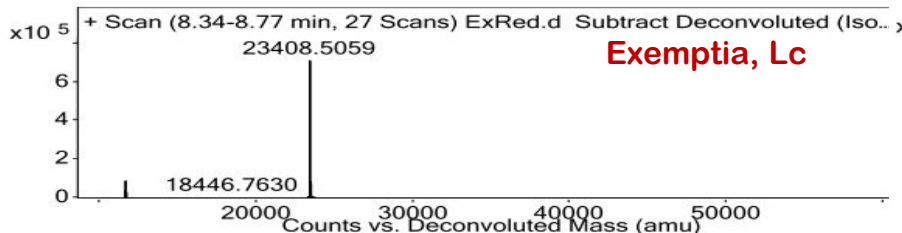
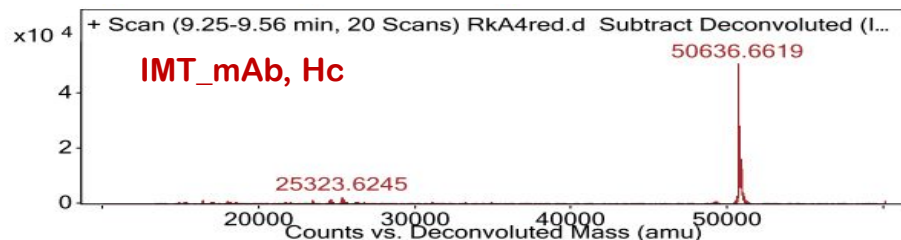
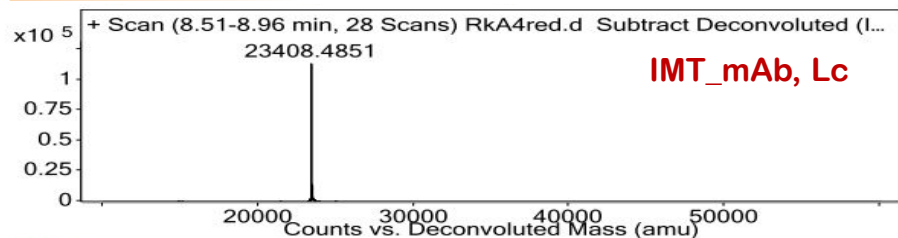
IMT_mAb



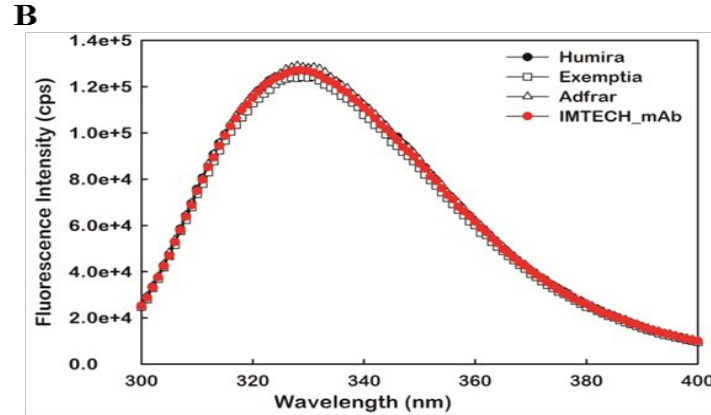
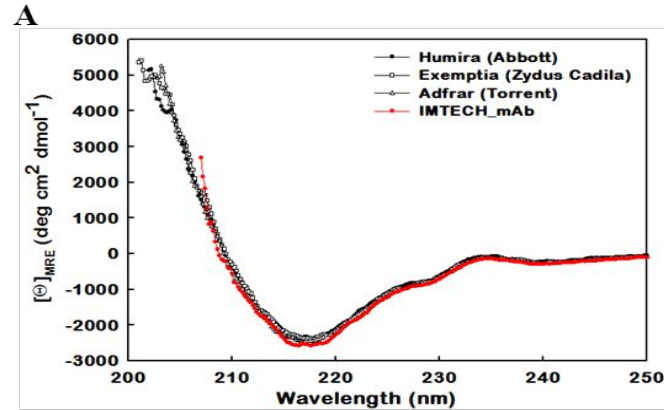
Confirms the correct molecular mass of Adalimumab.

Selected Data - Biophysical characterization

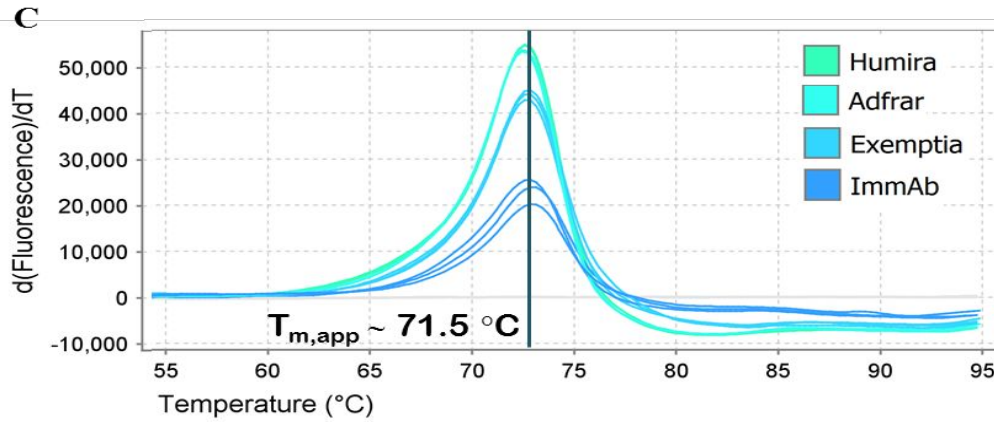
Mass spec analysis confirms IMT_C11 mAb contains single N-linked biantennary glycan in its heavy chain, similar to adalimumab and its known biosimilars.



Selected Data - Biophysical characterization



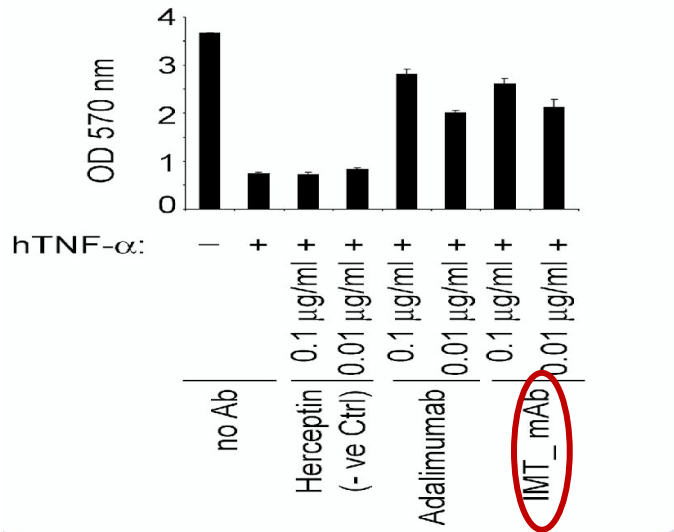
Comparison of (A) secondary structure by far-UV CD spectrum, (B) tertiary structure by fluorescence, and (C) thermal stability of purified IMT_mAb with that of commercially available anti-TNF α mAbs



In-solution secondary and tertiary structure and thermal stability results for IMTECH_mAb found similar to the Zydus's Adalimumab biosimilar Exemptia

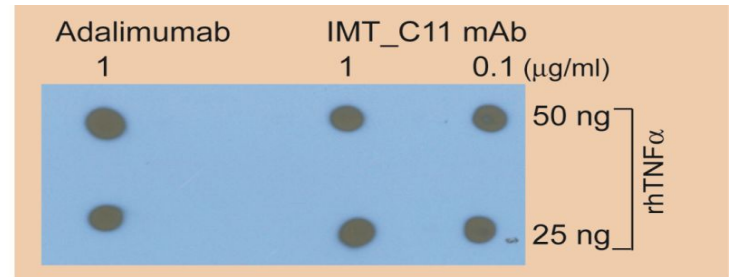
Selected Data - Biosimilarity: Neutralizing activity

hTNF α neutralizing activity



Preliminary results shows **comparable TNF α neutralizing ability and demonstrate biosimilarity of IMT_C11 mAb** with the originator molecule.

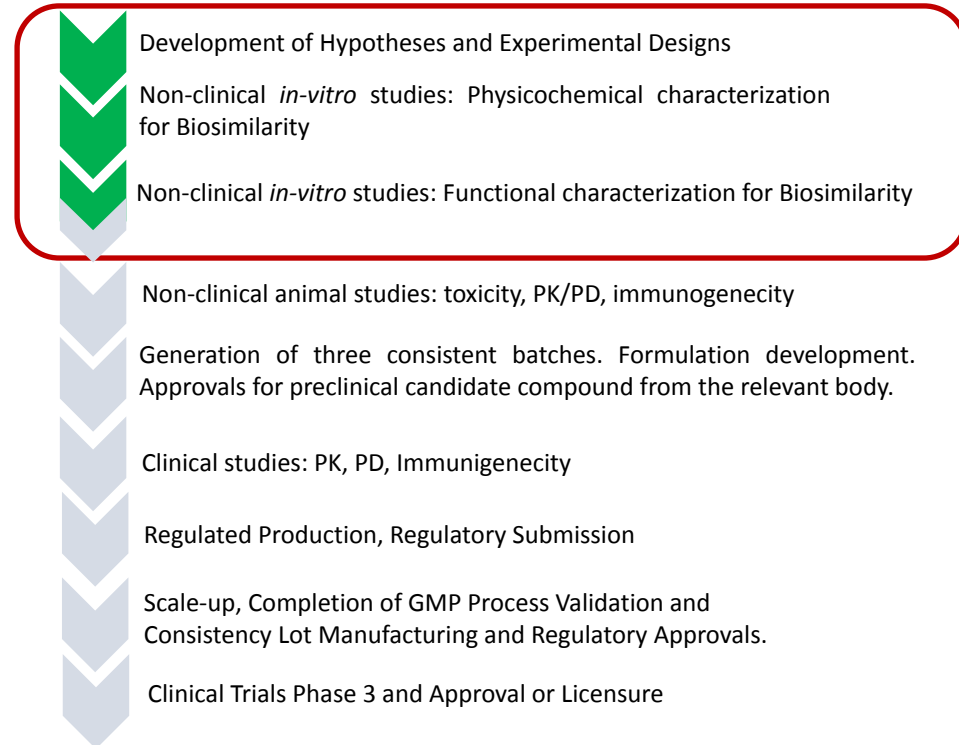
Dot blot assay for rhTNF α -binding



Cell-based assay for neutralization of rhTNF α -induced cell toxicity shows IMT_C11 mAb is **functionally equivalent** to Adalimumab

Current Status of Technology and Path Ahead

- Stage of Development
 - mAb production at shake flask level (unfed culture)
- Clone and construct developed inhouse (unencumbered)
- Vector and cell lines in-licensed from invitrogen
- Key process parameters —
 - IMT_C11 clone 100% purity
 - Yield: ~170-200 mg/L (100 ml culture vol. in 500 ml shake flask; unfed culture; repeated 3 times)



What are we seeking?

Seeking Industrial partners interested in:

- ❖ **Technology Transfer of clone:** IMTech shall license out clone IMT_C11 along with SOP's and protocols as per CSIR Tech Transfer Guidelines.
- ❖ **Co-development partners:** To carry out further development/validation work like functional characterization of biosimilarity and upscaling on mutually agreeable terms.
- ❖ **Sponsored R&D and research collaborations:** Any R&D program leveraging the capabilities at IMTech

Other Capabilities and Offerings

Other technology in the making

Molecule	Indication	Status
Pertuzumab	Treatment of metastatic breast cancer	At Initial stage
GCSF & peg-GCSF*	Chemotherapy-induced Febrile Neutropenia, Acute Myeloid Leukemia, Cancer Patients Receiving Bone Marrow Transplant, Peripheral Blood Progenitor Cell Collection and Engraftment, Severe Chronic Neutropenia	Process development for efficient protein purification & characterization

*Dr Sonal Datta, Project Scientist, CSIR-IMTech

Other R&D/knowhow capabilities available

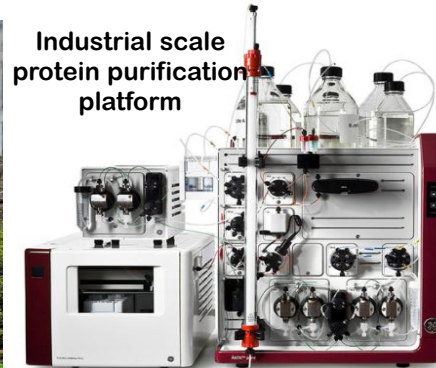
- Molecular Biology & mAb clone generation
- Process development and preclinical
- Analytical and characterization
- State of art mammalian cell culture and fermentation facility (up to 5L)
- High end protein analytical and downstream processing units

Facilities for BioPharma (for bacterial cultures only)

Equipped with **cGMP** and **validation compatible fermenters (5-500L)**, **Downstream processing equipment** such as centrifuges (batch and continuous), **Lab and pilot scale micro-/ ultrafiltration units**, cell disintegration systems, **Pilot and process scale chromatography systems** and analytical equipments etc.



cGMP Facility (DCGI approved)



Industrial scale protein purification platform



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For more information contact:

Case Manager:

Devanshi Patel
devanshi@venturecenter.co.in
+91-74100-45655

Lead Scientist:

Dr. Pradip Sen
psen@imtech.res.in
+91-9815171905

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