CHEMICAL GLYCOSYLATION OF PEPTIDES

BACHEM

PIONEERING PARTNER FOR PEPTIDES

GLYCOPEPTIDE APIs BY CHEMICAL SYNTHESIS

Goal is to improve physicochemical properties of peptides through selective glycosylation

- Both chemical structure and position of glycosyl moieties can markedly improve the biological activity of a peptide.
- A comprehensive library of glycans, containing human glycoproteins linked to asparagine, has been created.
- Well-defined glycosylated structures can be generated through chemical synthesis, which allows optimal choice of the glycosyl moiety and its position.

The partnership between Bachem and GlyTech is focused on the chemical development and manufacturing of glycosylated peptides.

Bachem has the proven expertise to scale up and manufacture kilogram scale peptides, while GlyTech is capable of producing glycans in kg amounts by a proprietary technology.

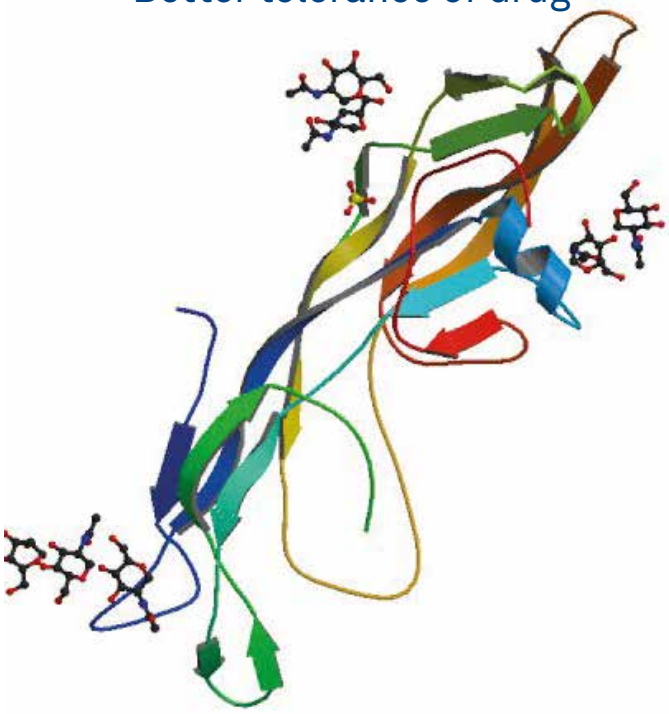
«The selective chemical glycosylation at large scale has potential to be applied to a variety of peptides, where we can pioneer the concept of improving current and future drugs via chemical glycosylation.»

Dr. José de Chastonay, CMO Bachem

WHY USE GLYCOPEPTIDES?

Glycosylation of peptide drugs can result in

- Increased half-life, providing extended dosing duration
- Better solubility, enabling improved formulation properties
- Improved response to therapy
- Better tolerance of drug



Human follicle-stimulating hormone, a 92 amino acid glycopeptide.
PDB: 1FL7
Fox, K.M., Dias, J.A., Van Roey, P. (2001) "Three-dimensional structure of human follicle-stimulating hormone", Mol. Endocrinol.15: 378-389

Traditional recombinant production of glycopeptides faces problems

- Heterogeneous glycopeptides
- Elaborate and costly purification, including removal of biological contaminants such as cellular debris or viruses

Advantages of chemical glycosylation

- Homogeneous products: Chemical synthesis yields well-defined glycopeptides
- Most chemically synthesized peptide drugs can be easily adapted to glycosylation
- Competitive production costs

ADVANTAGES OF GLYCOSYLATION

Selective glycosylation can improve the physicochemical properties of peptides

- Binding (Kd)
- Half-life
- Stability
- Homogeneity

As a result, this can have positive effects on pharmacological properties of a lead candidate

- Improved bioactivity
- Modified receptor selectivity
- Prolonged half-life

Selective, site-specific glycosylation leads to a homogeneous product with potential for more defined bioactivity compared to heterogeneous products.

Chemical glycosylation allows one to

- Attach any glycan at the desired position
- Specify the number of attached glycans
- Control the glycan structure

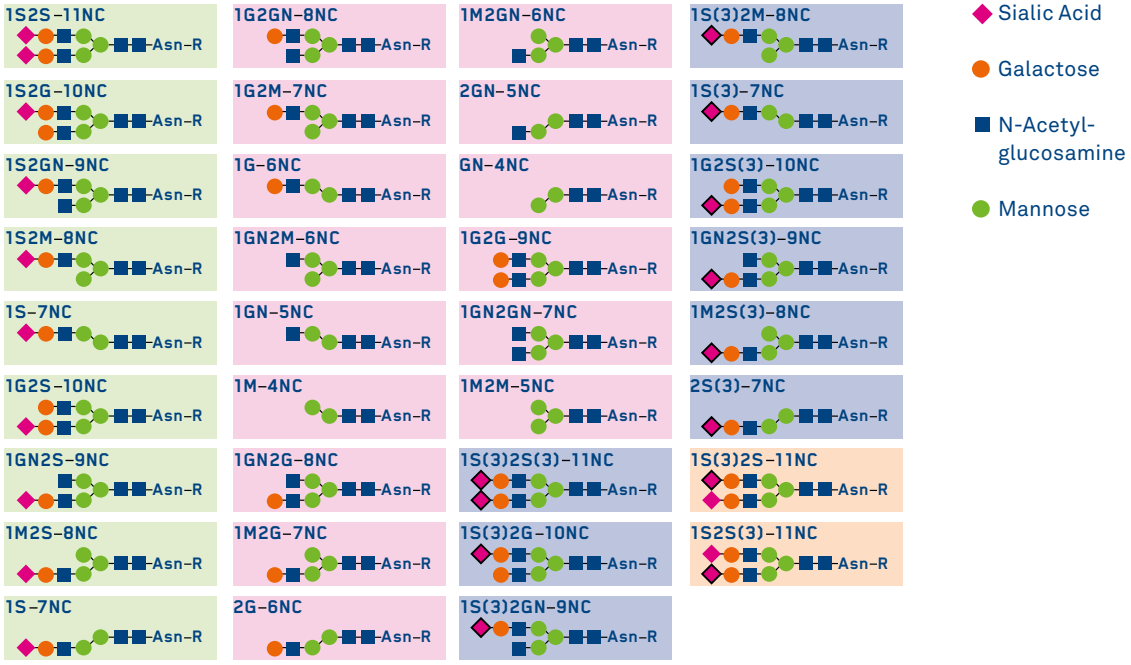
«Glycosylation can improve the pharmacokinetic profile of drugs.»

OUR SERVICE

Generating a library of glycosylated analogs can be a powerful way to enable optimization of lead candidates.
This is achieved by a «library» approach:

- For a lead peptide, which has been chosen for glycosylation, a human type glycan library is available.
- The optimized glycopeptide designs will be selected in a joint project team of the client together with Bachem and GlyTech, to benefit from the respective expertise.
- Synthetically glycosylated peptides will be produced in small scale (mg-g) by GlyTech.
- The glycosylated peptides will be screened by the client in order to find a glycopeptide with improved pharmacological properties.
- A glycopeptide with enhanced properties can then be scaled-up and manufactured by Bachem in the required quantities.

More than 50 glycans are available



A TYPICAL PROJECT OUTLINE

LEAD OPTIMIZATION

- Compound properties not satisfactory
- Definition of current compound properties
- Identification of desired compound properties

DESIGN PHASE

- Scientific dialogue and collaboration between partner and Bachem/GlyTech
- Design a number of compounds expected to meet desired properties

SYNTHESIS & SUPPLY

- Synthesis of compounds at milligram or gram scale for research purpose (non-GMP)
- The compounds get supplied with the agreed sequence, structure and quantity

TEST PHASE

- Positive results may lead to a License Agreement.
- Results may lead to another iteration of Design Phase for further improvement of the lead compound

SCALE-UP

- Scale-up and analytical development at Bachem
- Manufacturing according to cGMP

«Numerous glycopeptides, including glyco-somatostatin analogues and glyco-GLP-I analogues have been synthesized.»

PROOF OF CONCEPT
Interferon β-1a

Chemically synthesized Interferon β-1a compared to the recombinant compound:

- Less heterogeneity (no glycoforms)
- Extended half-life
- Improved *in vitro* binding
- Enhanced *in vivo* efficacy
- Synthetic process optimized for industrial manufacturing by Bachem

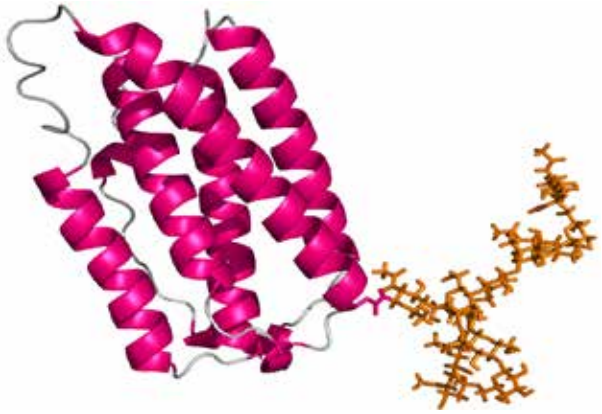
Implications of chemically synthesized glycopeptides:

- Widens the scope of peptide optimization beyond simple amino acid sequence
- Improves approved drugs which fall short
- Aids challenging new drugs in development
- Leads to increased intellectual property value

The complex chemical synthesis of Interferon β-1a was adapted to cost-effective industrial-scale manufacturing.

Bachem
and GlyTech, Inc.

Two pioneers in their respective fields collaborating to advance innovation in drug development.



Interferon β-1a is a glycosylated 166 amino acid protein and an approved drug substance to treat multiple sclerosis with a world market of more than $ 4 billion. There are currently three recombinant products on the market which are mixtures of at least 10 glycoforms.

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GLOBAL BUSINESS

Bachem facilities are located in Switzerland, the EU, and in the USA.

All cGMP manufacturing sites are inspected by the US-FDA and national authorities.

CPHI INNOVATION AWARDS

Bachem Holding AG and GlyTech, Inc. were 2013 CPhI innovation prize finalist for the groundbreaking work on Interferon β-1a.

The technology has been used in multiple other projects, such as to manufacture glycosylated somatostatin analogues and glycosylated GLP-1.

In all cases, drug improvements were achieved.

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