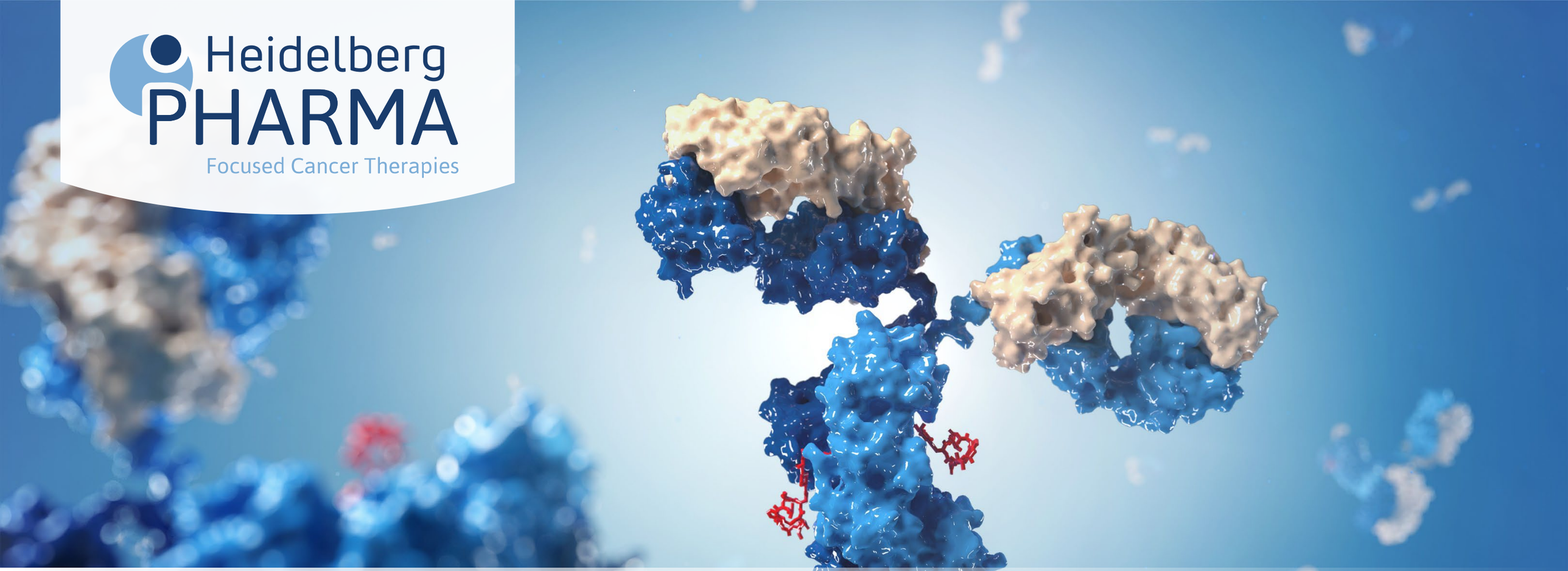
Presentation BOS Basel

08 June 2022

Dr. Christian Lutz
Heidelberg Pharma

Dr. Thomas Schlatterer
CARBOGEN AMCIS

Heidelberg PHARMA
Focused Cancer Therapies



Discovery & Development of a New ADC

June 2022

Heidelberg Pharma at a Glance

Developing new options to address major challenges in cancer therapy

Our Company

WILEX AG becomes Heidelberg Pharma AG

Frankfurt Stock Exchange: WL6

Shares outstanding: 34.18 million

Market cap: ~€170 million

Headquarters: Ladenburg, Germany

100 employees (May 2022)

Our Mission

Improving efficacy

Overcoming resistance mechanisms

Killing dormant tumor cells

New options in cancer therapy

Our Approach

New mode of action in cancer therapy - Antibody Targeted Amanitin Conjugates (ATACs)

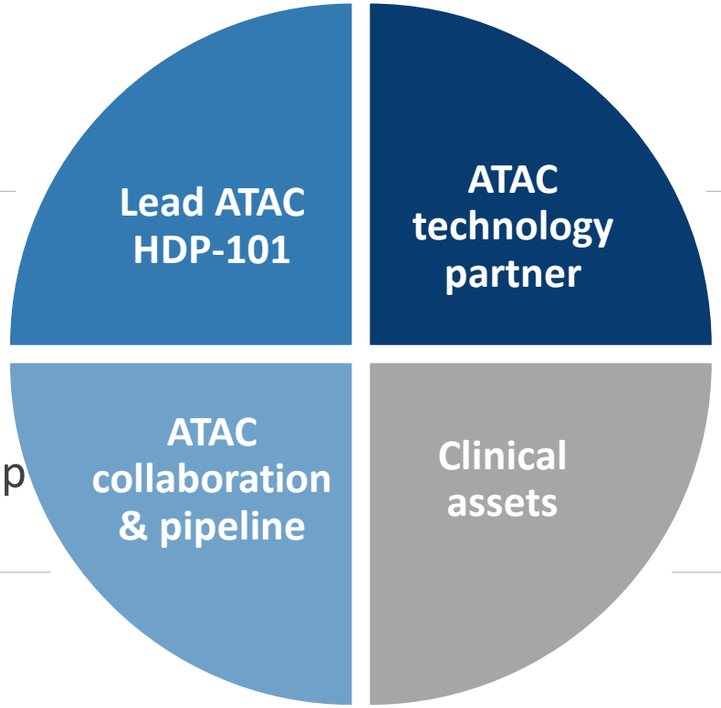
- Induction of apoptosis by inhibition of RNA Polymerase II
- Application of innovative payload harnessing ADC technology

Strategic Cornerstones

Build proprietary ATAC pipeline	Sign technology licensing collaborations	Additional upside potential with partnered non-ATAC legacy clinical assets

Proprietary lead candidate
HDP-101

Heidelberg PHARMA



ATAC technology partnering with pharma and biotech

Heidelberg PHARMA

ATAC cooperations & follow-up proprietary ATAC candidates

Heidelberg PHARMA

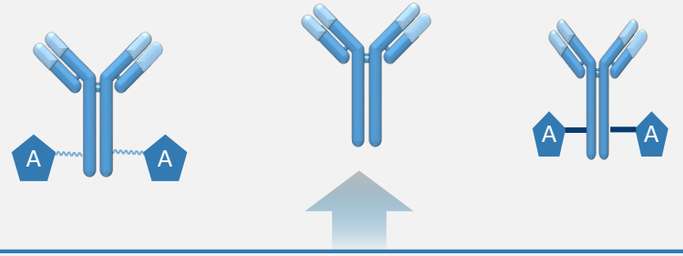
MESUPRON®
REDECTANE®
RENCAREX®

WILEX AG

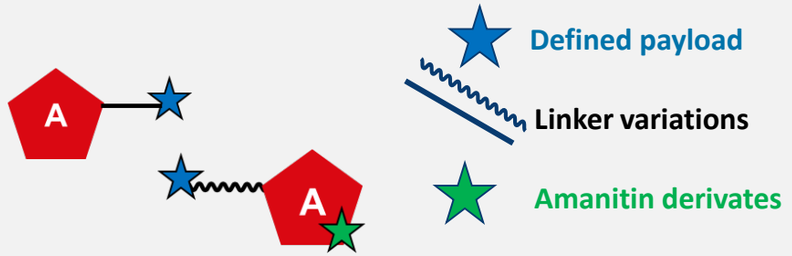
Early Validation and Cash Through Pharma Collaborations + Future High Value Potential with Proprietary Portfolio

Partnering target by target

Antibodies from partners, license to the partner, development by the partner



ATAC toolbox:
customized and target-optimized toxins and linkers

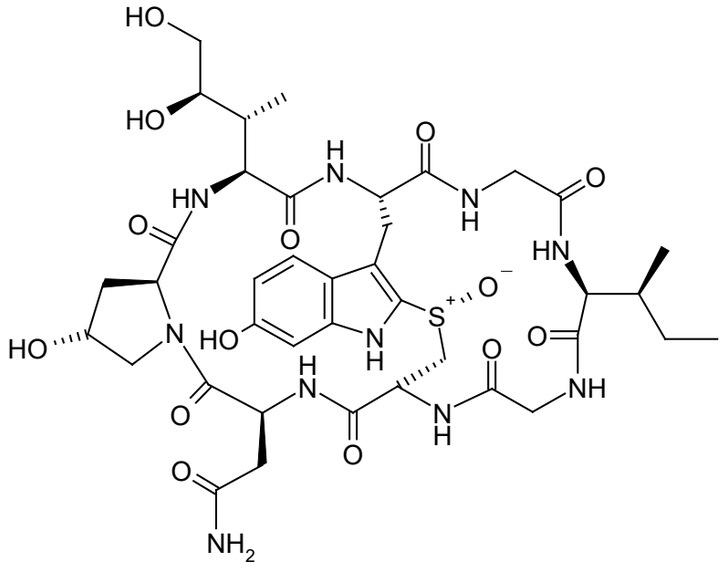


In-licensed antibodies, internal development activities

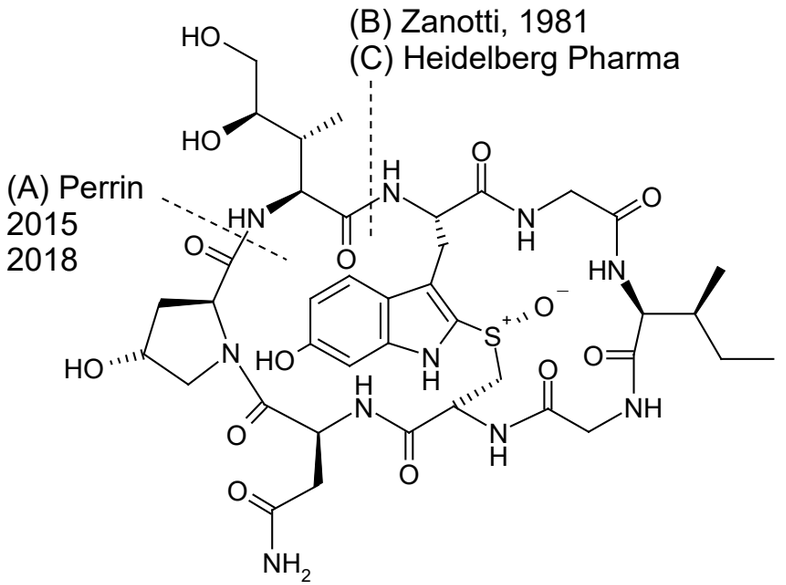
Proprietary

α-Amanitin Retrosynthesis

- **Systematically studied since 1941**
- **Structurally resolved in 1977 (beta-Amanitin)**
- **Synthesis and SAR with Ile as DHIL surrogate since 1981 (Zanotti)**
- **Total synthesis by Prof. Perrin, Prof. Süßmuth groups and Heidelberg Pharma**

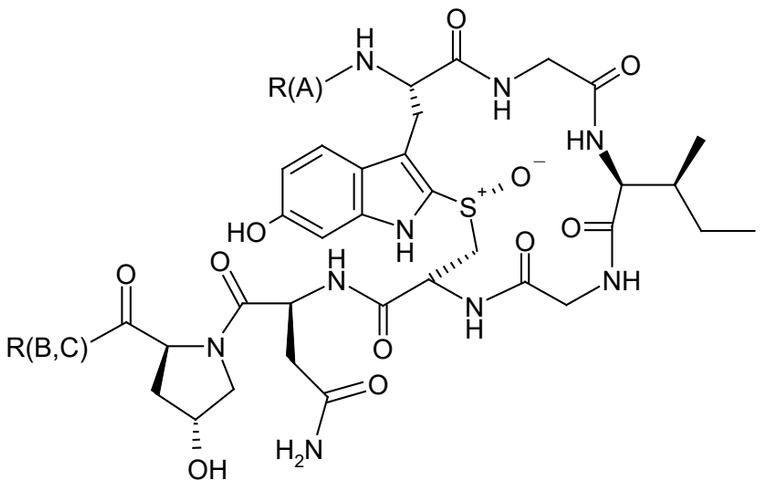


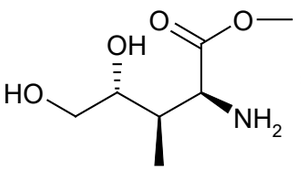
α-Amanitin Retrosynthesis

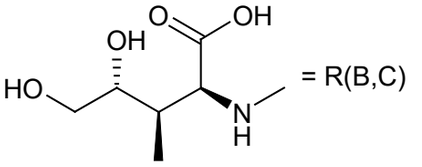


Macro-

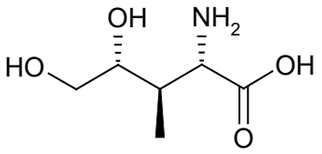
Lactamization



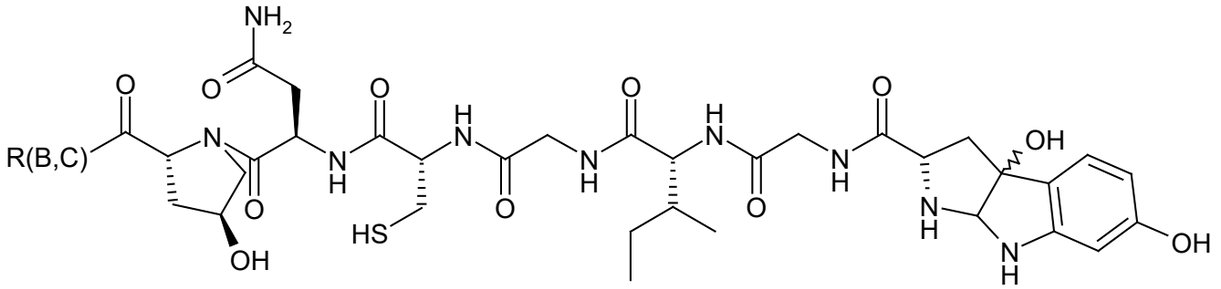


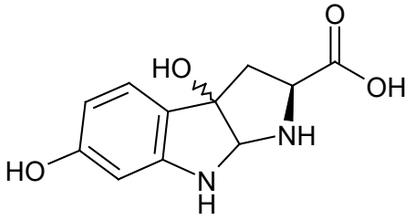


Savige-
Fontana
Reaction



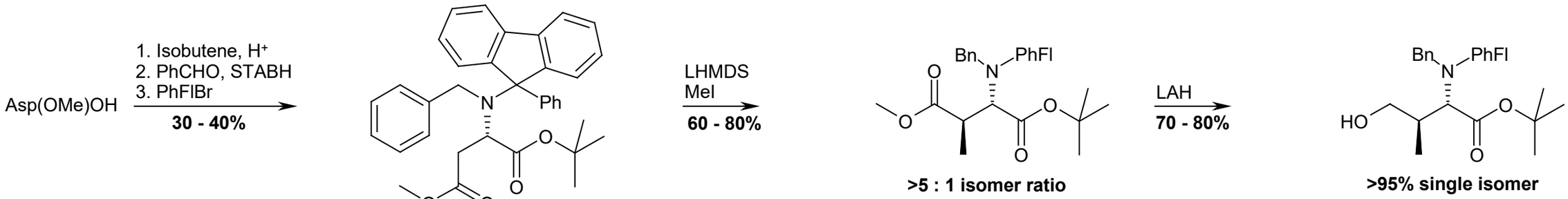
(2S, 3R, 4R)-4,5-dihydroxy-isoleucine (**DHIL**)

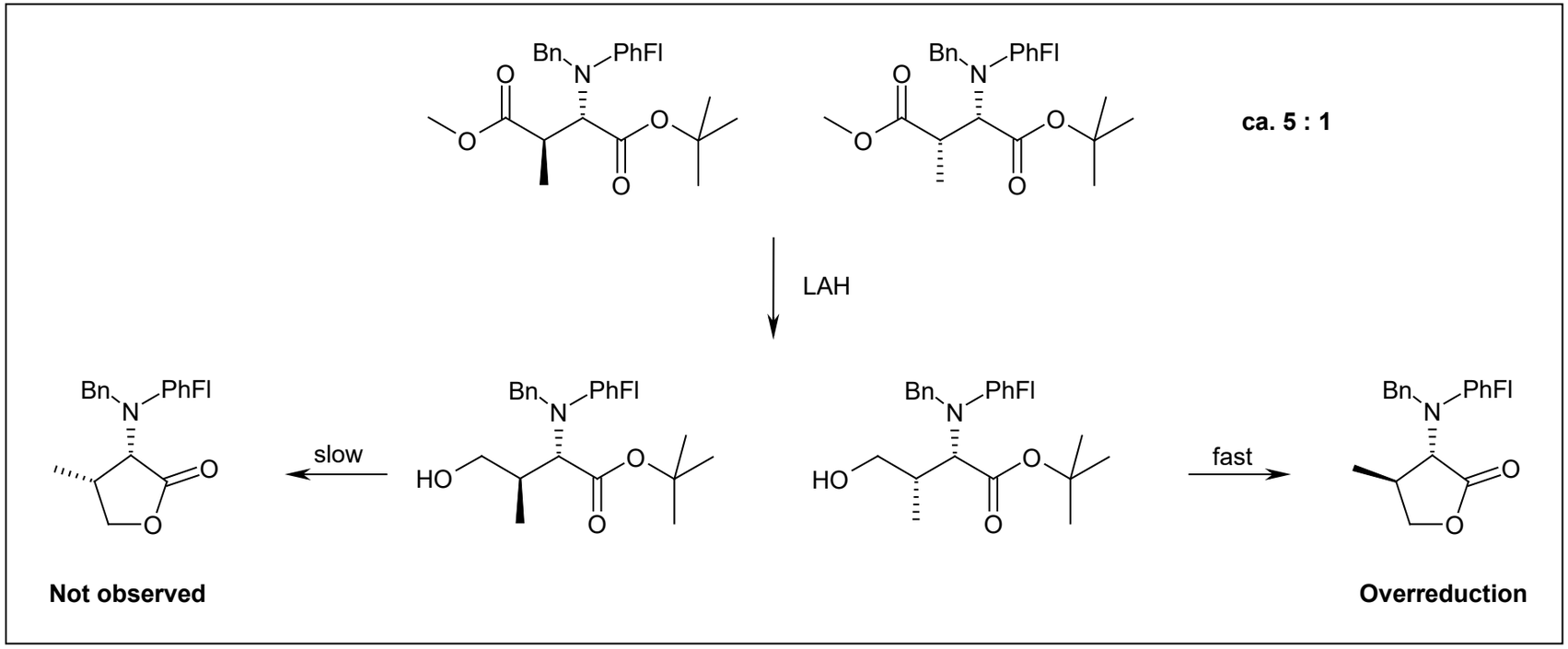




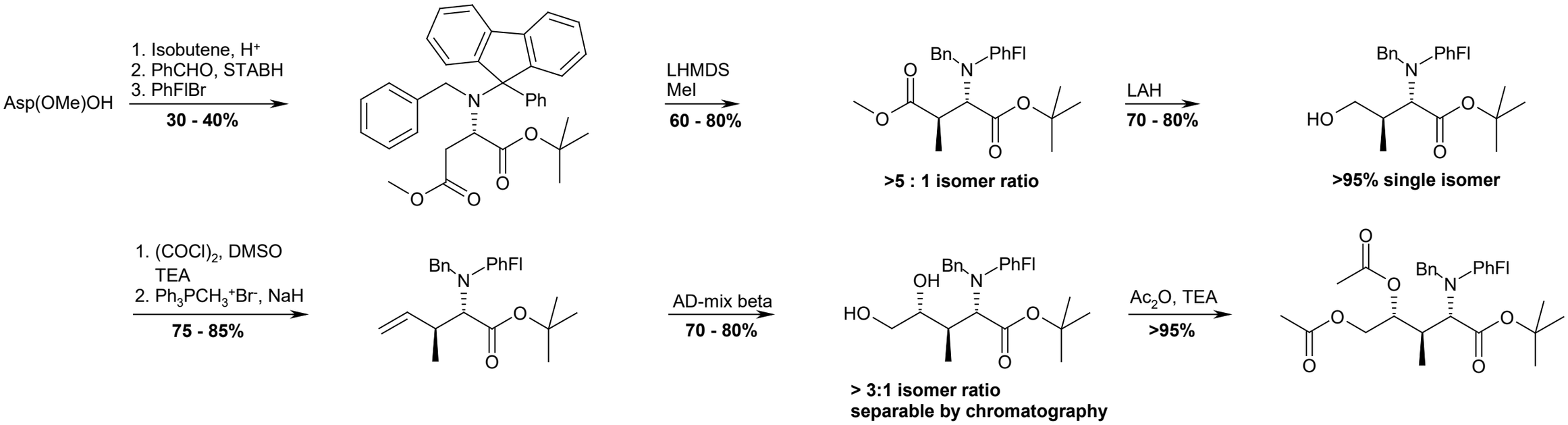
3 -hydroxyhexahydropyrrolo[2,3-]-indole-2-carboxyl (**Hpi**)

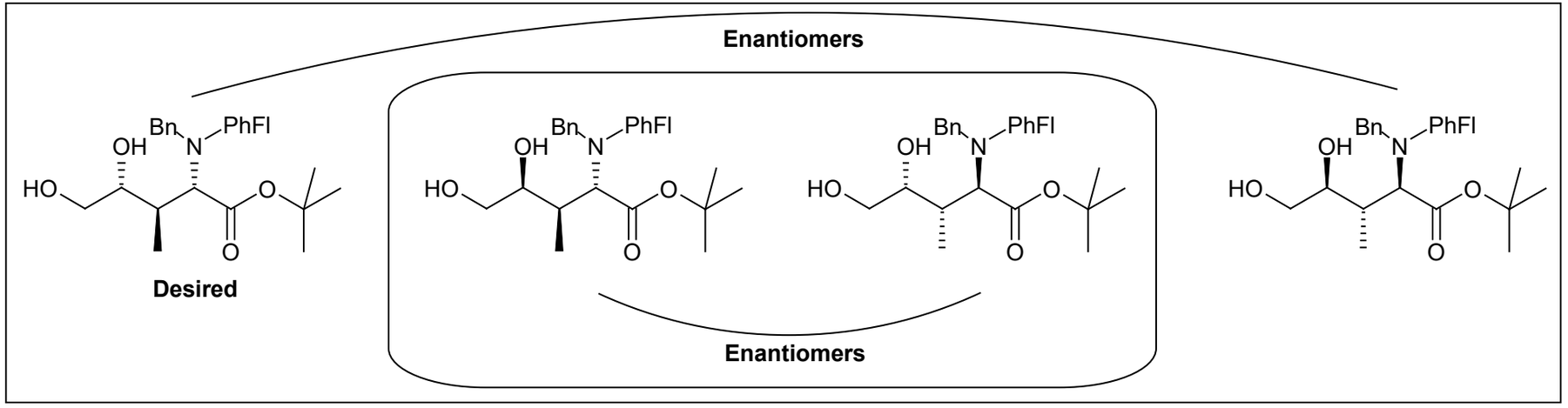
Dihydroxysoleucine Synthesis



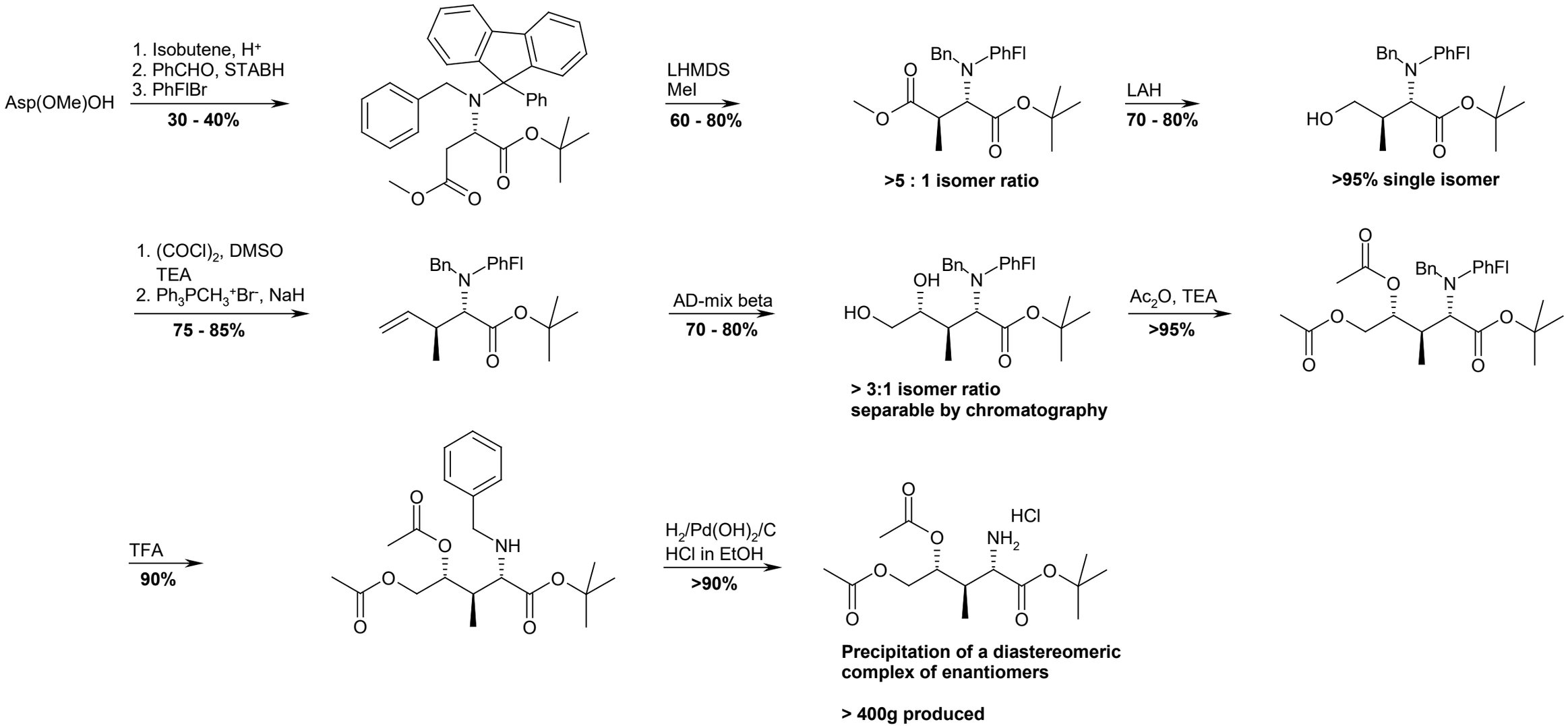


Dihydroxysoleucine Synthesis

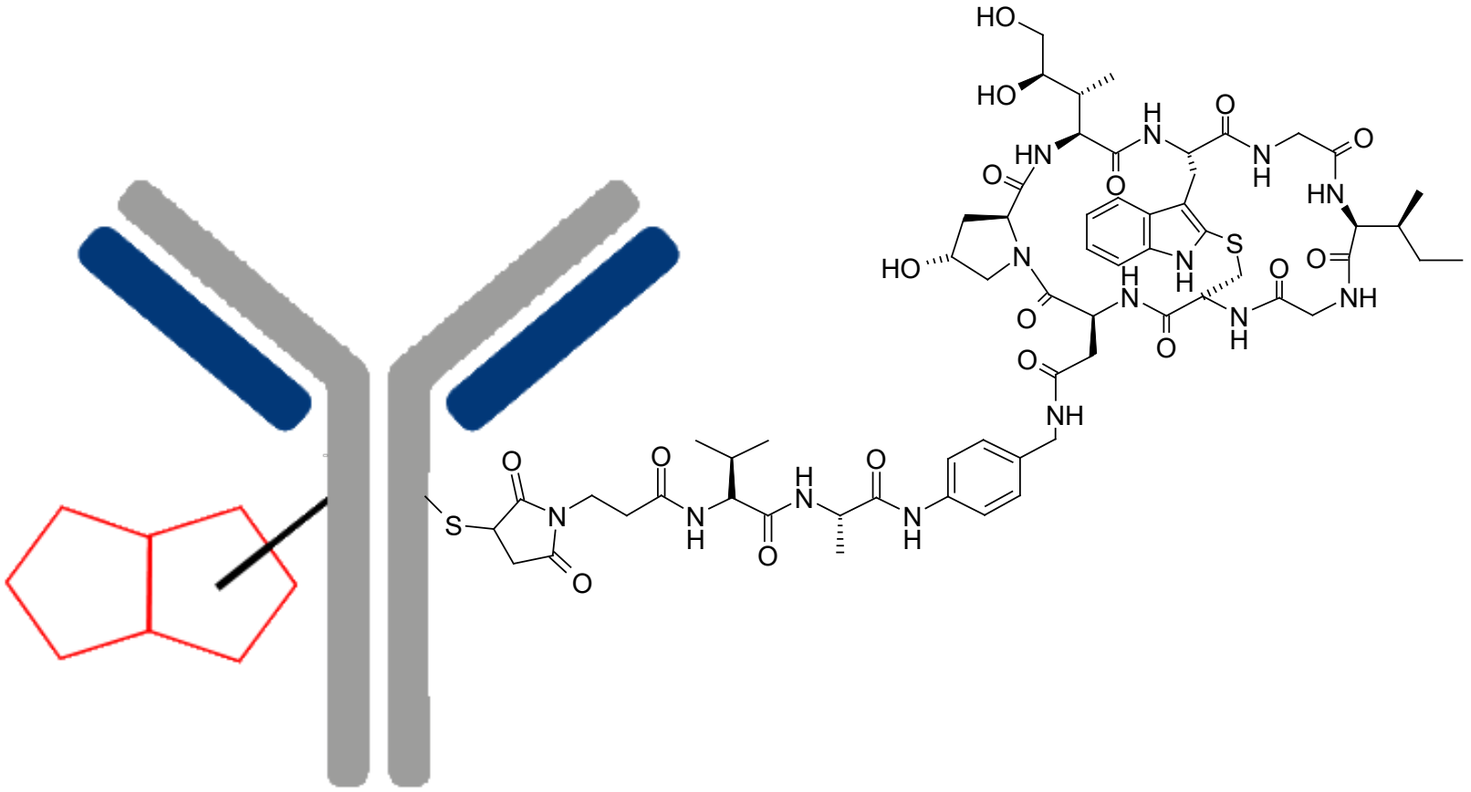




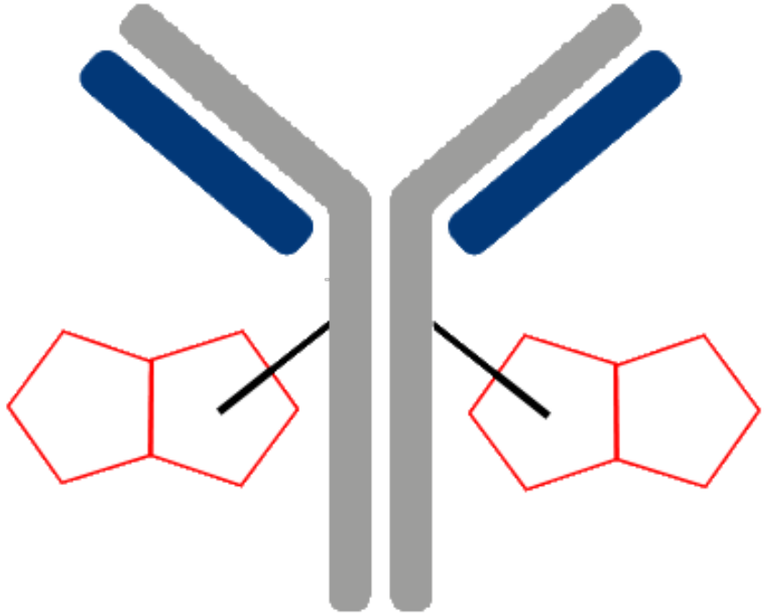
Dihydroxysoleucine Synthesis

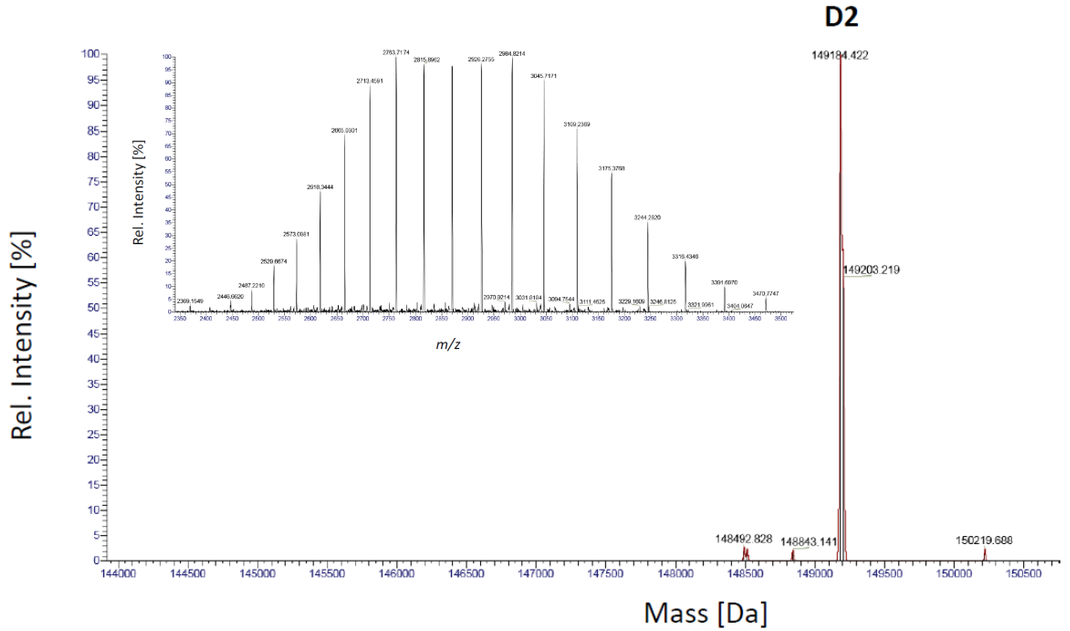


HDP-101 Site Specific Conjugation



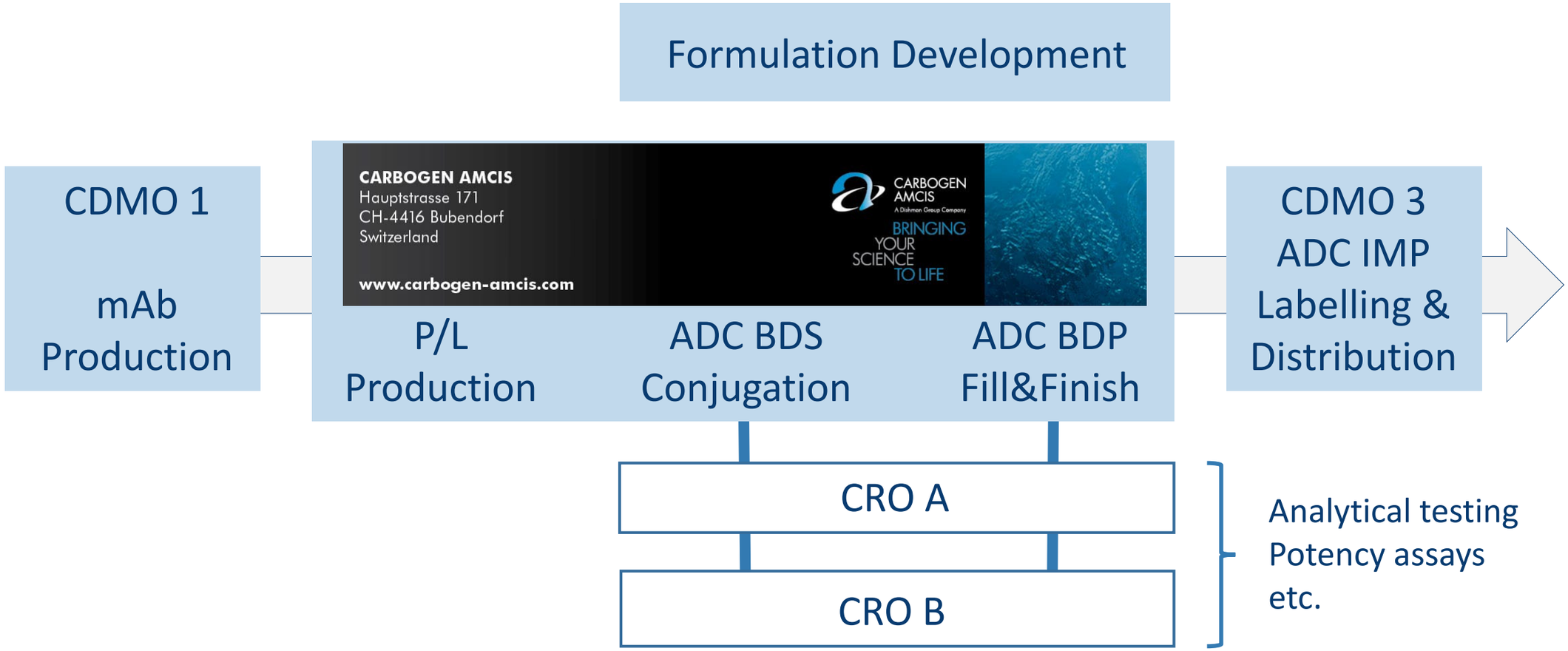
HDP-101 Site Specific Conjugation





- **Site-specific maleimid conjugation**
- **DAR 2**
- **Lysin, interchain and others available**

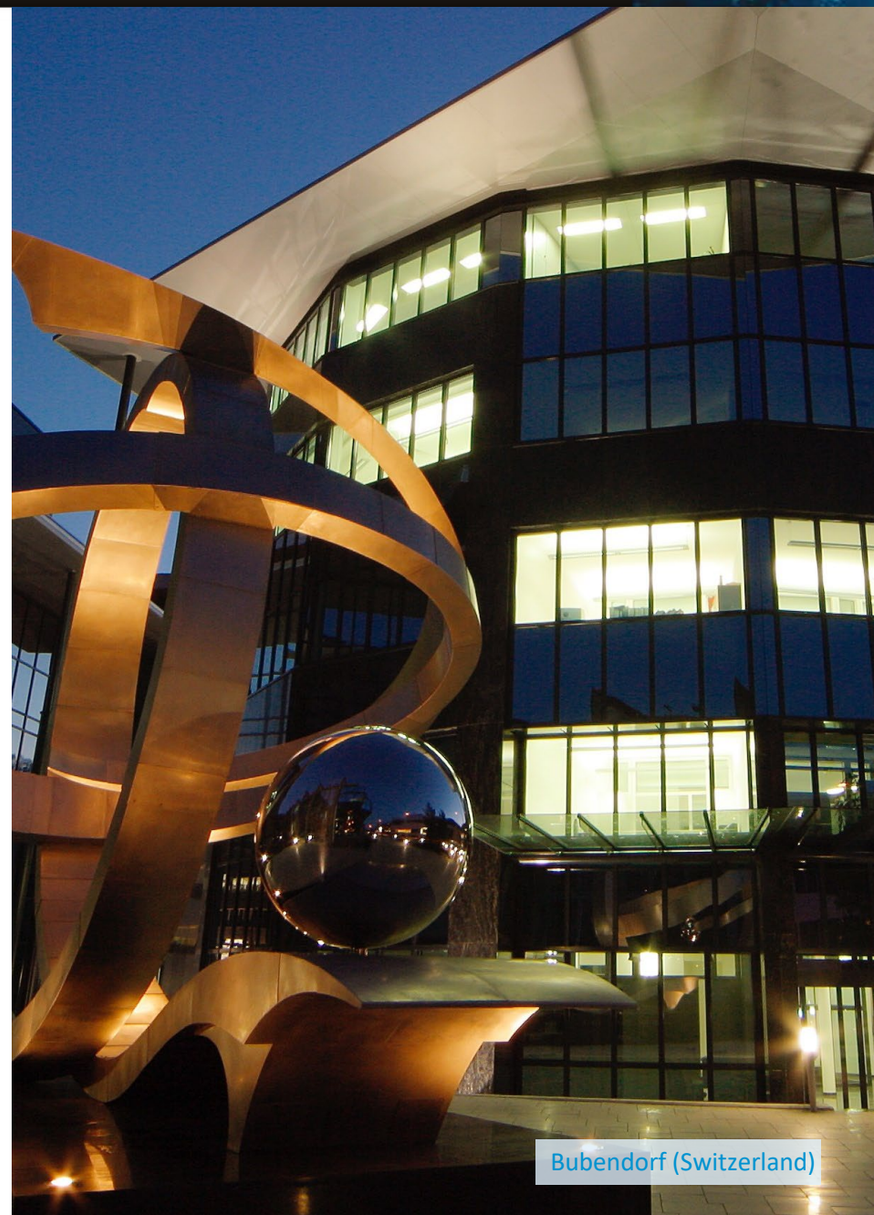
HDP-101 CMC Development & Clinical Supply



CARBOGEN AMCIS
Company Overview

CARBOGEN AMCIS Key Facts

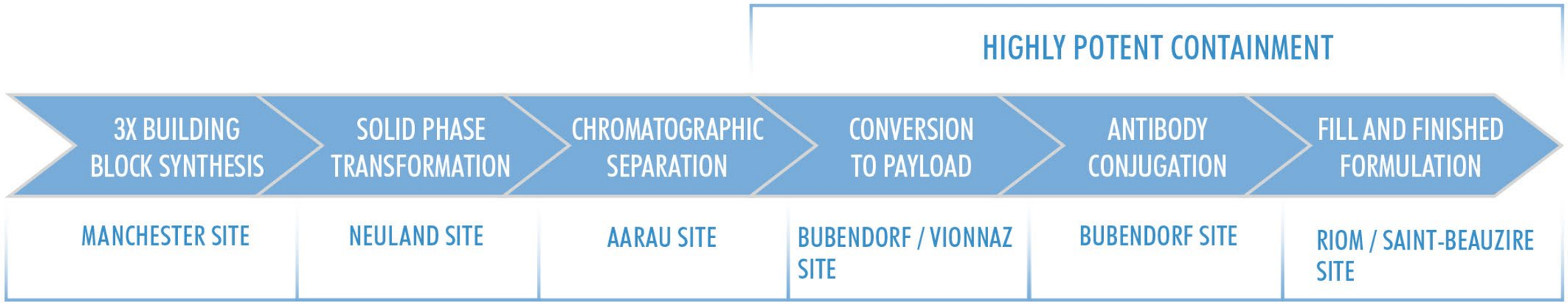
- Over 30 years experience
- Global presence – manufacturing sites
  - 4 x Switzerland
  - 1 x United Kingdom
  - 2 x France
  - 1 x The Netherlands
  - 1 x China
- Over 250 chemists, with > 40% Ph.D.
- More than 150 complex projects per annum
- 32 commercial products (customer's IP)
- More than 40% are HiPo projects
- Highly successful audit history



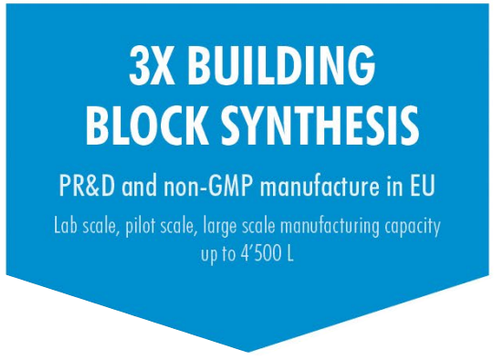
Bubendorf (Switzerland)

Our Locations Global & BOS booth 18

Mastering the Supply Chain – HDP101



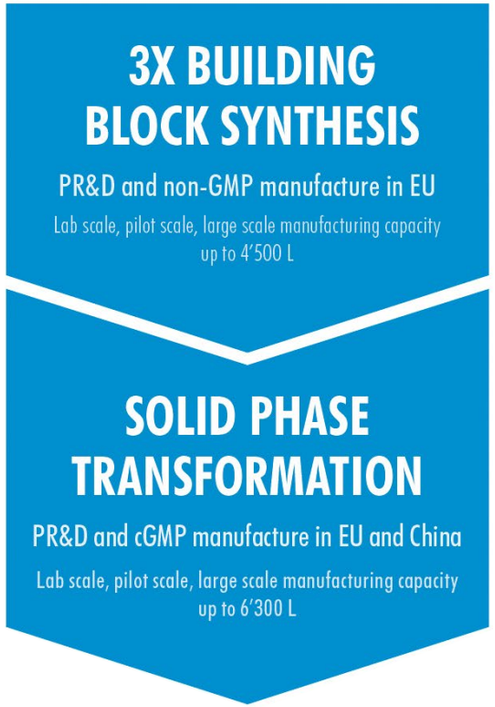
Mastering the Supply Chain – Step by Step



MANCHESTER SITE

- 10 Production vessels, 85 to 4500 L
- Cryogenic reactors 250 L & 3000 L
- High temperature reactor 400 L
- Pressure reactors (3 bar, 250 L & 3000 L)
- Temperature range: -100°C to +160°C
- 100 kg silica gel chromatography column
- **Biotage (40 kg silica)**
- **Photoreactors**
- ISO22716 Cosmetics GMP Standard

Mastering the Supply Chain – Step by Step

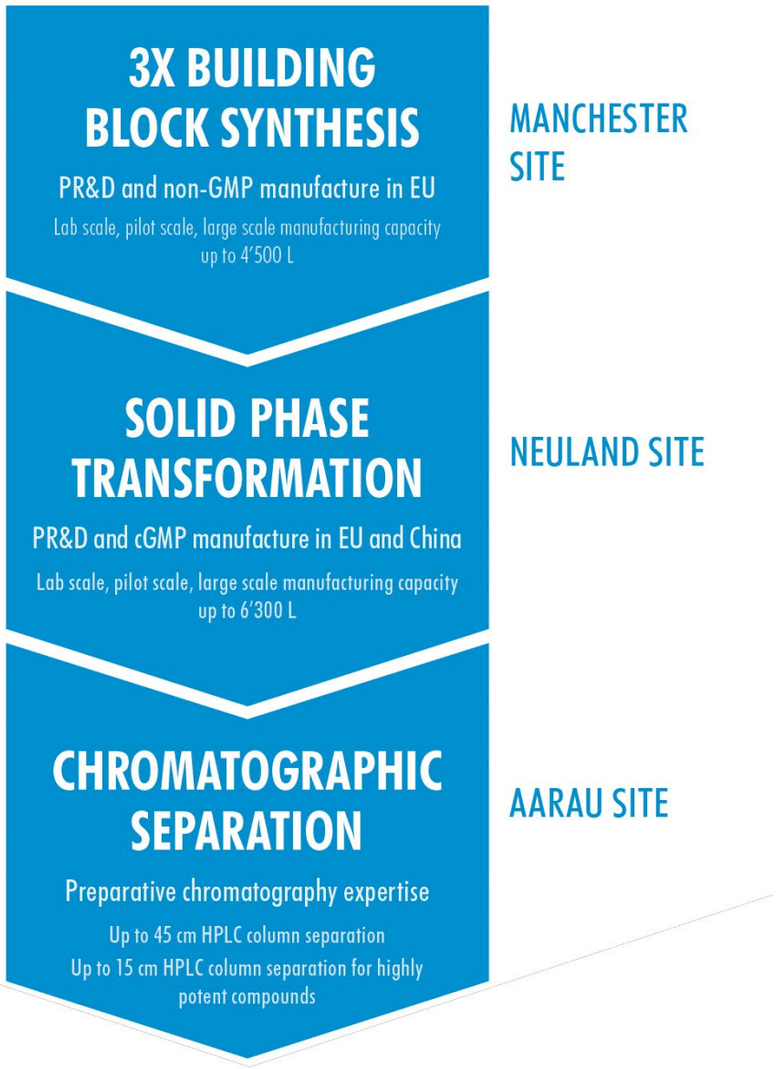


MANCHESTER SITE

NEULAND SITE

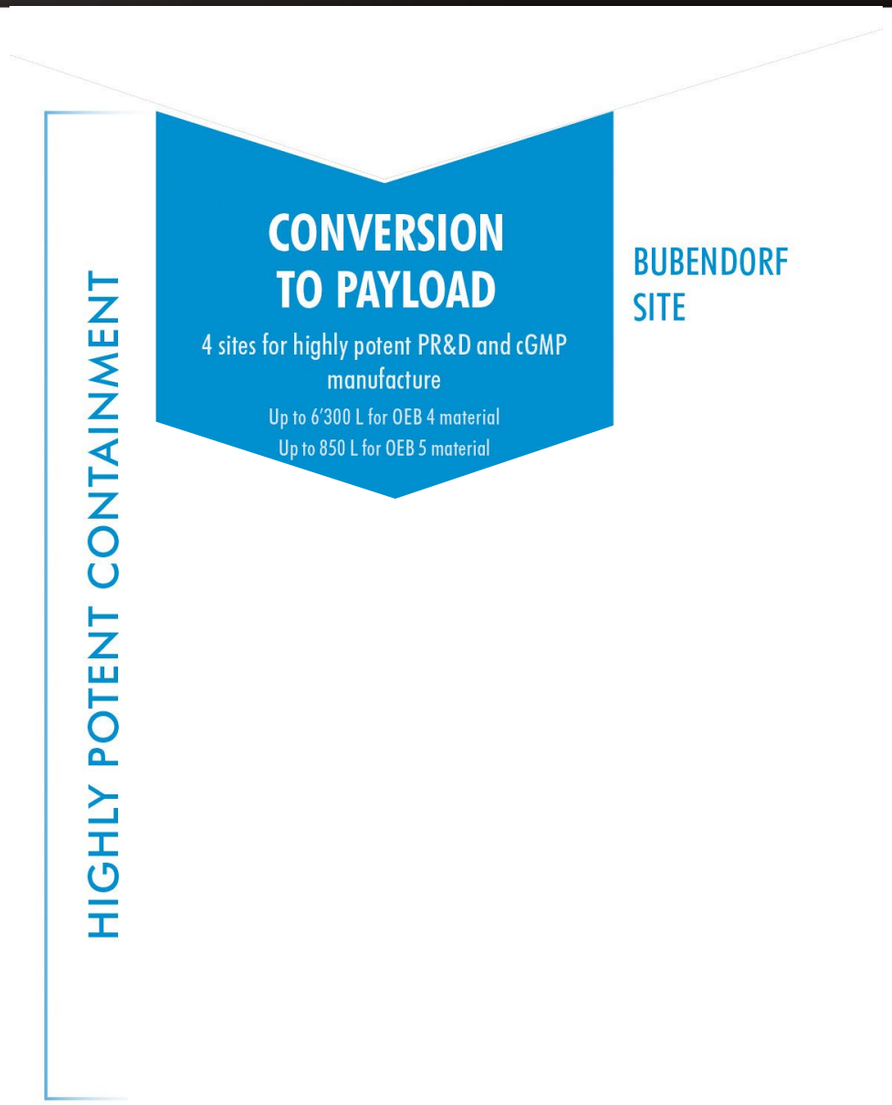
- Process development up to category 3
- Crystallization development (particle size control, polymorphism etc.)
- Hydrogenation development
- Pilot plant manufacturing up to category 3
- Commercial manufacturing of niche products up to 640 L & Chromatography up to 15 cm and Biotage
- In-house stability chambers
- **Solidphase synthesis for ADC drug linker**

Mastering the Supply Chain – Step by Step



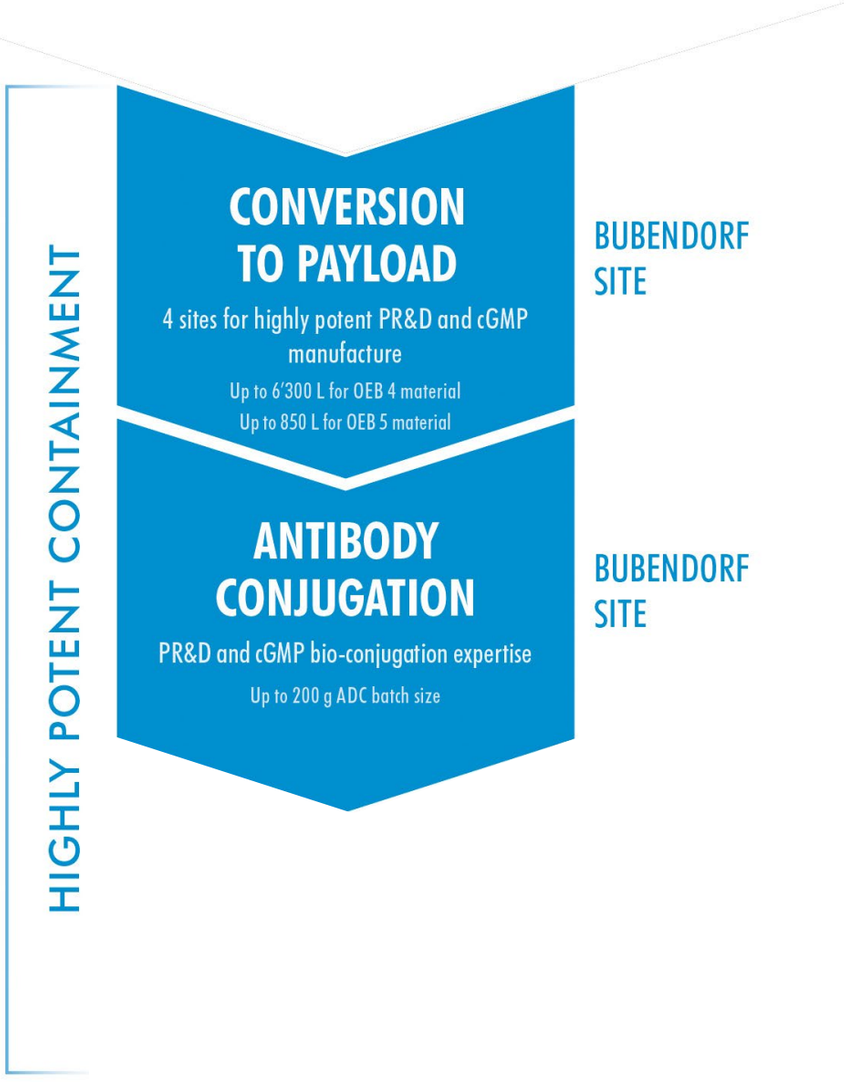
- Process development up to category 2
- **cGMP chromatography up to ID 20 cm** including NF/TFF for concentration
- SMB purification
- Scale-up to pilot plant scale & commercial manufacturing of niche products up to 640 L
- Safety evaluations of critical reactions
- Particle size engineering by wet-milling

Mastering the Supply Chain – Step by Step



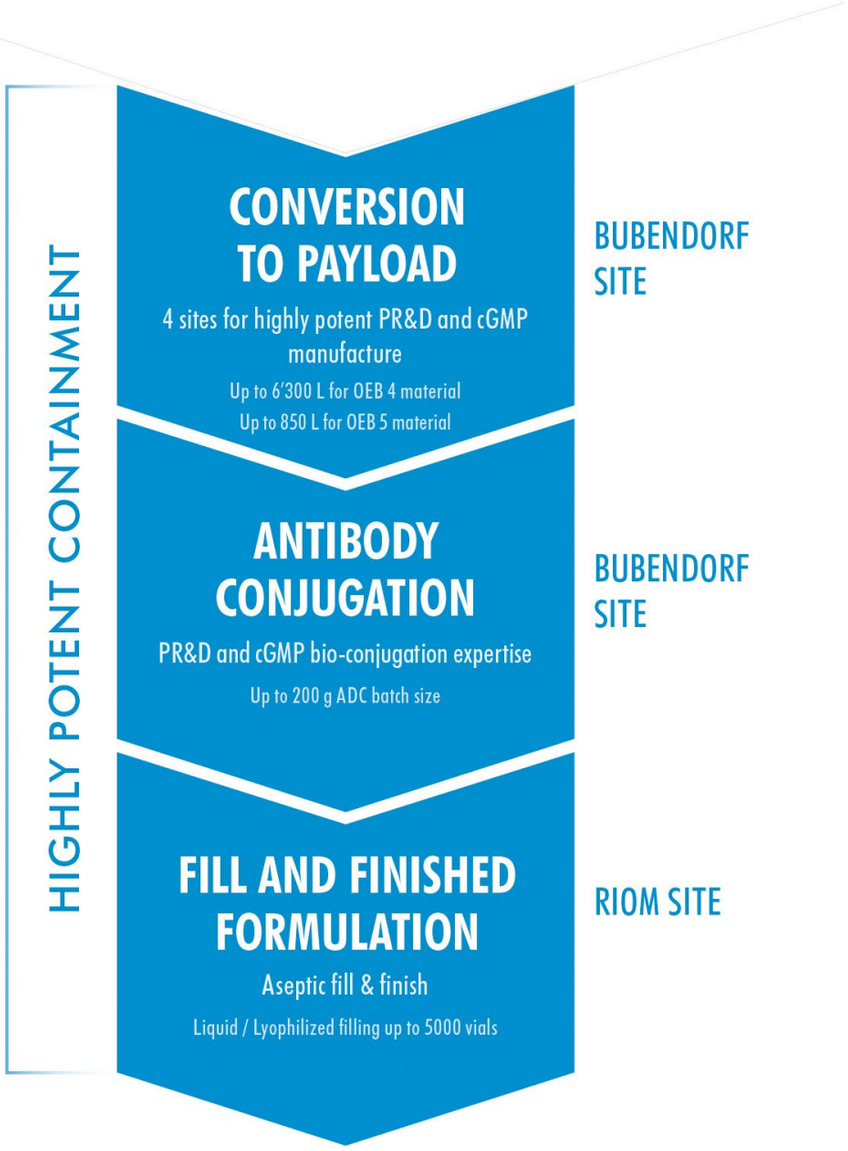
- Process development up to category 4+
- Safety evaluations of critical reactions up to category 4+
- Small scale cGMP manufacturing of Highly Potent APIs & intermediates Pilot plant manufacturing up to category 4+ up to 250 L
- **cGMP chromatography up to ID 45 cm, Highly Potent APIs up to ID 15 cm**
- Commercial manufacturing of niche products up to 2500 L
- NF/TFF available for downstream processing

Mastering the Supply Chain – Step by Step



- Preconjugation modification of biological molecules
- cGMP process development and manufacture of warheads and linkers
- OEL < 10 ng/m3 8h-TWA
- Conjugation of mAb/biologics to small molecules and polymers
- Cysteine/Lysine/ Conjugation
- Enzyme & Protein Mediated Conjugation
- Solution Phase & Solid Phase Conjugation
- Capacity up to 20 l volume (aqueous systems)
- Chromatography
- Tangential Flow Filtration (TFF)
- Formulation Screening: Avacta Optim 2
- Purification capabilities

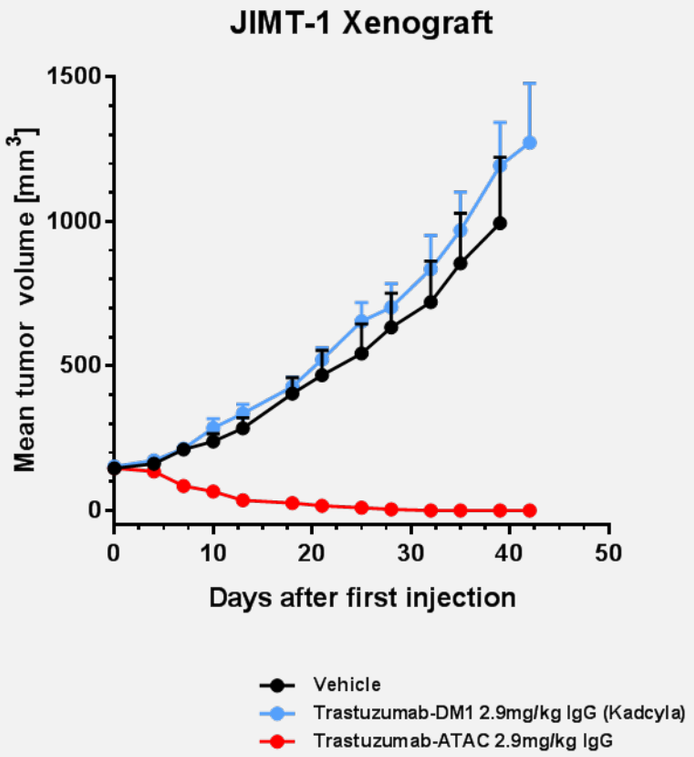
Mastering the Supply Chain – Step by Step



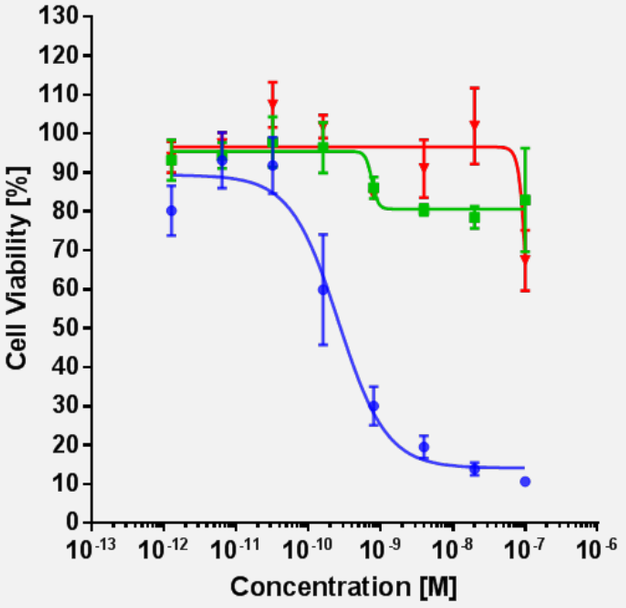
- Line 1: Liquid and lyophilized forms – Vials only
- Line 2: Liquid only – Vials, Prefilled Syringes and Cartridges
- Technology: Skan (isolators), Bausch + Ströbel (filling lines), HOF (lyophiliser)
- Filling line: up to 3,600 units per hour
- Lyophilizer: starting with 30,000 units – max batch size up to 45,000 units over 2 shifts
- Packaging format : Vials from 2R to 100R & Prefilled syringes from 1 to 10ml
- Special features:
  - HiPo API (incl. Toxins)
  - Aseptic formulation
  - Viscous products
  - Low temperature
  - Inert atmosphere

Therapeutic Advantages of ATACs: Effective on Dormant Cells, Breaking through Drug Resistance and Relapse

ATACs are active in resistant or difficult-to-treat tumors



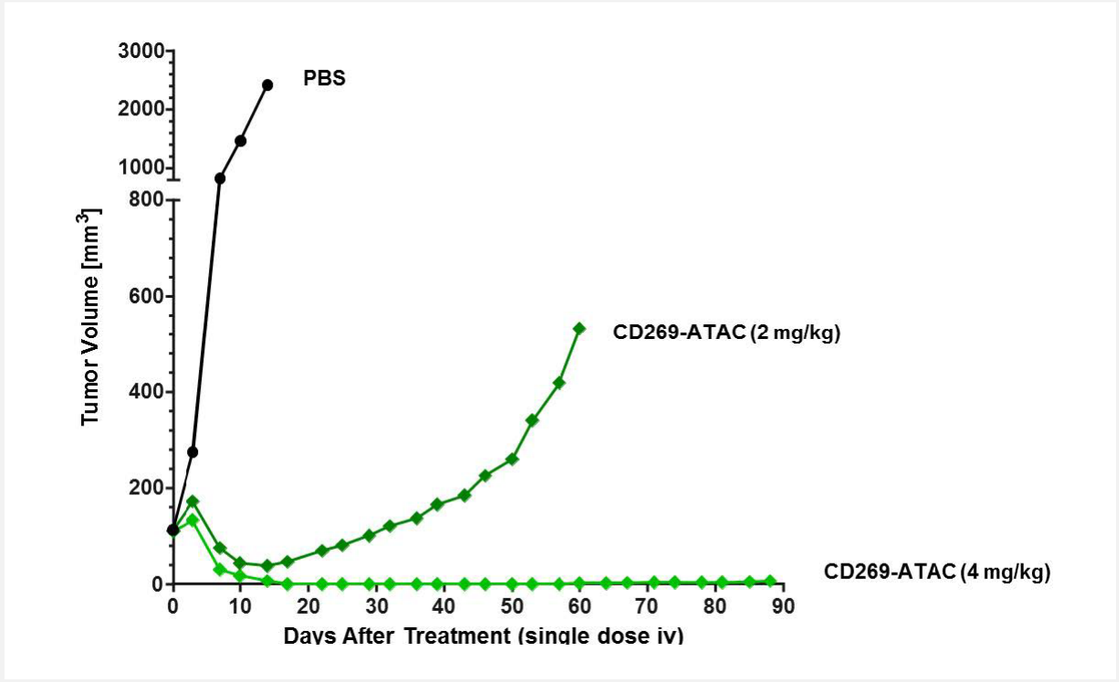
ATACs are highly potent on true, non-dividing embryonic stem cells



ATAC	IC50 (nM)
Anti-EpCam Amanitin ADC	0.26
Anti-EpCam DM1 ADC	Not detectable
Anti-EpCam MMAE ADC	Not detectable

HDP-101: Strong Efficacy in Multiple Myeloma Xenograft Models

Complete tumor remission in a subcutaneous multiple myeloma mouse model

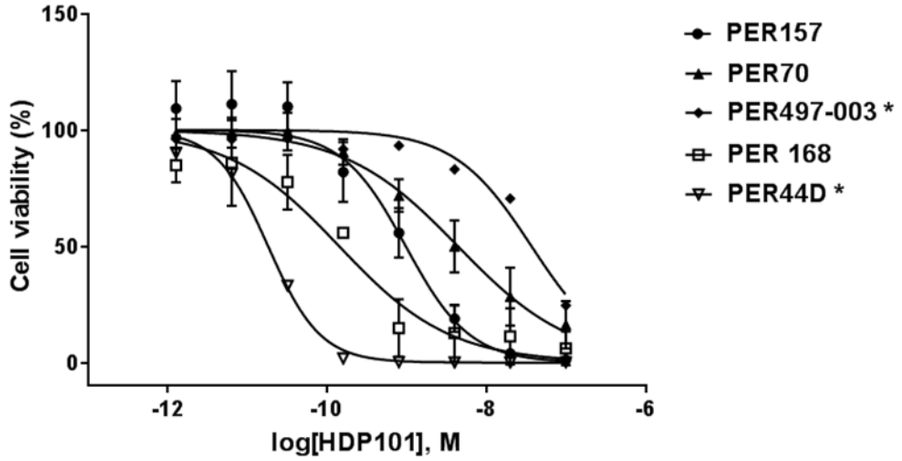


- Subcutaneous NCI-H929 murine xenograft model for multiple myeloma
- Animals were treated with a placebo (PBS) or a single dose of HDP-101
- Very good safety & tolerability profile after multiple dosing in various species
- No liver toxicity seen

At 4 mg/kg a complete remission was achieved for 3 months

HDP-101: Efficacy on Multiple Myeloma Patient Cells

Efficacy of HDP-101 on primary cells isolated from Multiple Myeloma patients even on low BCMA expressing cells



MM cells	PER157	PER70	PER497-003 *	PER 168	PER44D *
LogIC50	-9.01	-8.354	-7.43	-9.845	-10.74

Patient	BCMA copies /cell
PER 157	6015
PER 44D	1967
PER 70	2262
PER 168	273

- Primary CD138+ cells were isolated from MM patient bone marrow biopsies
- Correlative assessments (Analysis of relative BCMA expression in a large cohort of MM patients)

- Cooperation with M.Raab DKFZ (German Cancer Research Center), Heidelberg

Summary

- Successful establishment of a fully synthetic route to Amanitin payloads
- Establishment of a secure and reliable supply chain based in Europe
- 3 Different Amanitin payloads are available for partnering
  - α-Amanitin, β-Amanitin or Amanin based
  - Stable or enzymatically cleavable linkers
  - Different Amanitin attachment sites
- Site-specific antibody conjugation established
- Lyophilizate for parenteral application
- HDP-101 is in clinical phase I development (multiple myeloma)

Thank you!

Dr. Christian Lutz
Heidelberg Pharma

Dr. Thomas Schlatterer
CARBOGEN AMCIS