mAbs
ANTIBODIES
FOR MEDICINE

THE HIGHWAY TO
mAb drug candidates

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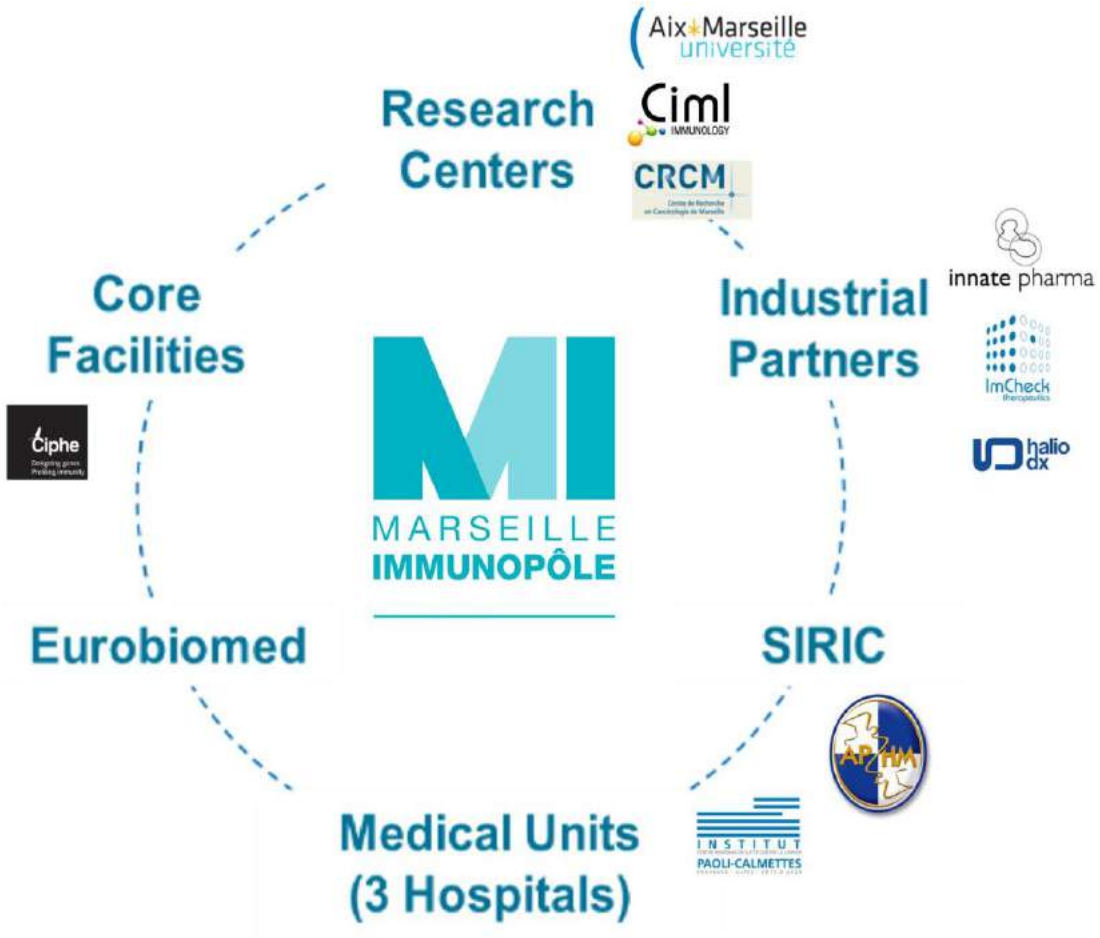
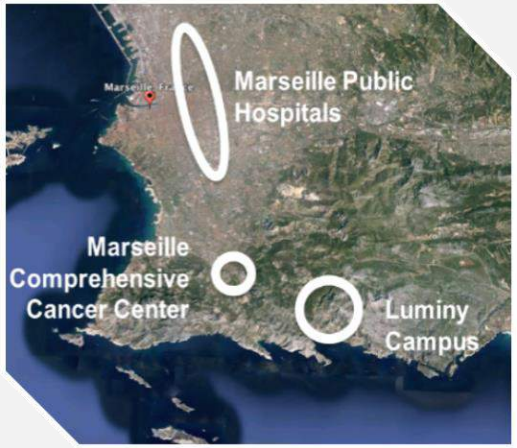
Founding shareholders

LOCATED WITHIN THE MARSEILLE IMMUNOPOLE (MI)

A scientific environment dedicated to immunotherapy





MImAbs CSO discovered and/or participated to:

- Development of 6 mAbs now in clinical development (Lirilumab, Monalizumab, Lacutamab, anti NKG2D, CD39, CD73)
- Licensing/co-development with Novo Nordisk, BMS, AstraZeneca
- Numerous early development packages of mAbs currently in preclinical development (naked, and ADC) within Innate Pharma and MImAbs

MISSION : FROM TARGET IDENTIFICATION TO PRECLINICAL DEVELOPMENT IN IMMUNOTHERAPY

A fully integrated fee for service platform for antibody-based therapeutic development in cancer & inflammation

Target Identification

Preclinical Proof of Concept

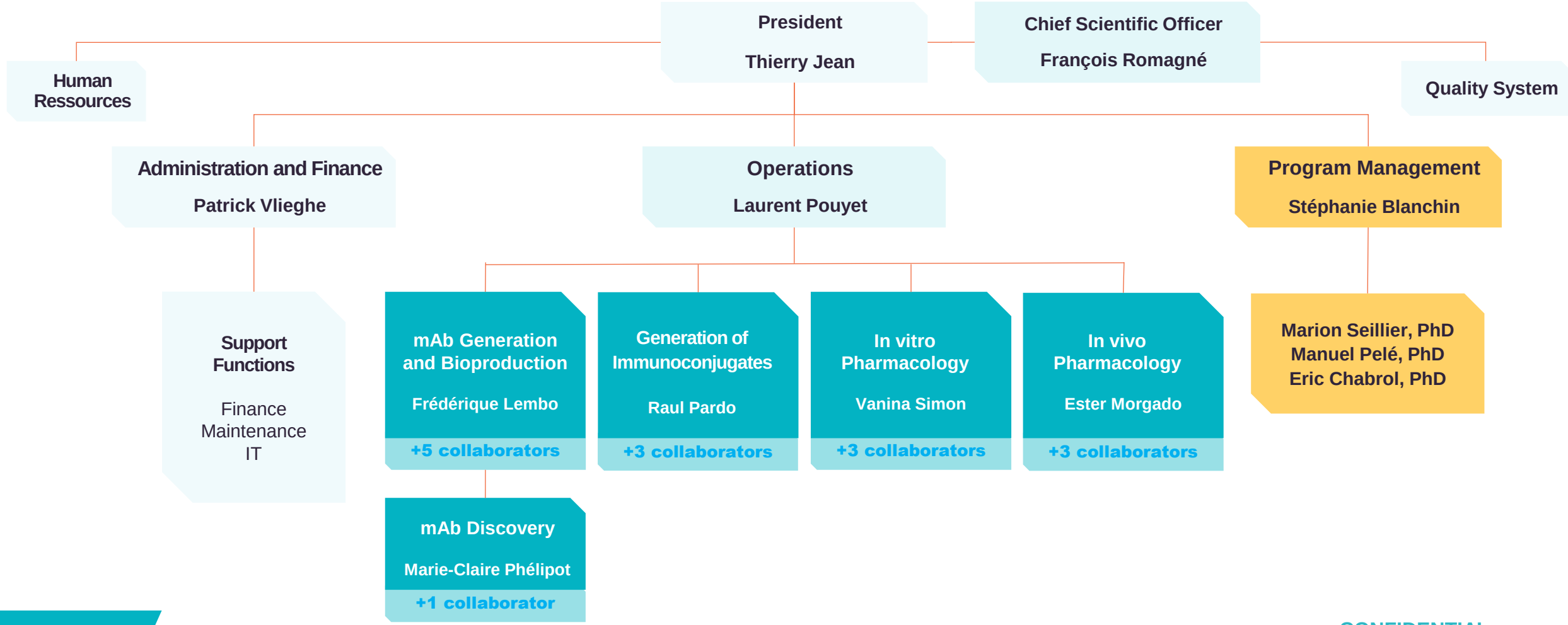
- mAb Lead Candidate Generation, Selection & Engineering
- In vitro and in vivo Immunopharmacology Validation

GMP Preclinical Development

TARGET SOURCING
Academic & industrials network

DELIVERABLE
Antibody candidate compatible with pharma development
Pharmacological package

ORGANIZATION



MImAbs SCIENTIFIC TRACK RECORD & PARTNERSHIPS

- **More than 100 immunizations programs** (tools and drug candidates)
  - **~20 target validation programs, 16 naked mAbs, 3 ADC, 1 bispecific mAb**

Packages in development in Pharma/Biotech

- **Transferred to clinical development**
  - **1 naked mAb : CD39 in-licensed by AZ**
- **Transferred to regulatory driven development**
  - **2 naked mAbs (Innate Pharma) : CD73, Siglec**
  - **1 Bispecific (NK engager) (Sanofi) : Undisclosed**
- **Close to regulatory driven development**
  - **3 ADC : MICA, NKp46, undisclosed**

- **Other achievements**
  - **Significant contribution to the creation of start-ups EmergenceTherapeutics, Kalsiom**
  - **13 publications in peer reviewed journal : Cell, Cell report, Immunity…**
  - **1 new tool for bispecifics : a human CD3e KI mice model**

- Main clients (current)
  - EmergenceTherapeutics
  - Kalsiom
  - Innate Pharma
  - Domain Therapeutics
  - Imcheck Therapeutics
  - Egle Therapeutics

Others undisclosed

mAbs
ANTIBODIES
FOR MEDICINE

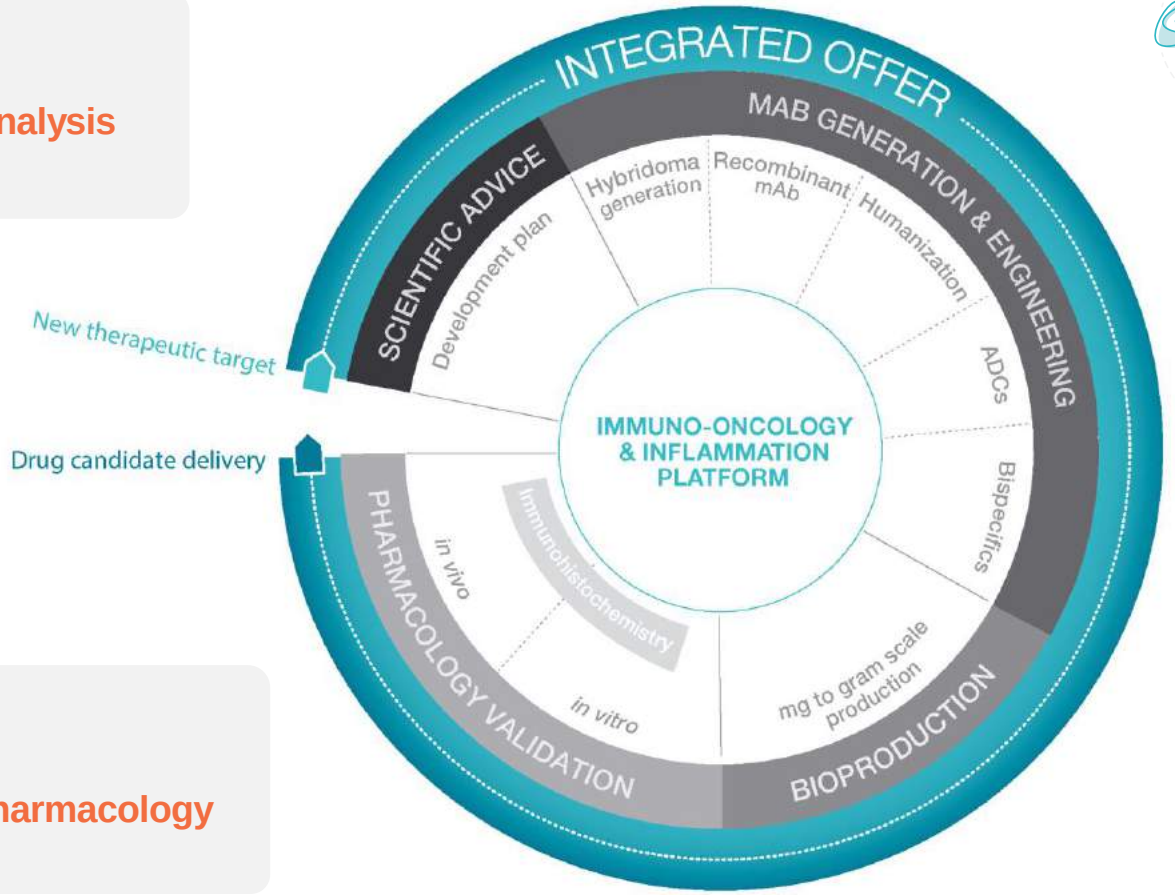
Scientific and Technical Expertise

Full Program Overview

Drug Candidate Identification Roadmap

STEP 1
Project analysis

STEP 2
Generation and Selection of Lead Candidates



STEP 3
Antibody engineering

STEP 4
Bioproduction

Step 5
Immunopharmacology

RECENT AND CURRENT INNOVATION PROGRAMS

- **Certification by Alloy Therapeutics for the use of humanized GX mice (human IgG genes)**
  - Robust immunization
  - Mouse model validated by several pharmaceutical industry
  - Original research license terms: development milestones, but no royalties
  - Client must partner with Alloy TX before working with MImAbs on GX mice
- **mRNA Immunization**
  - Feasibility in progress for 6 different antigens (including ‘usual’ antigen, GPCR, ion channels)
  - Facilitates immunization for difficult antigens
  - Finalization of validation Q1-2022
- **Implementation of Beacon single cell technology to avoid hybridoma step and increase screening depth**
  - Functional screening at the level of single cell (40 000 individual B cells)
  - Significant reduction in turnaround time to obtain superior recombinant hits
  - Implementation in January 2022
- **Stable transfection package to obtain high expressing mini-pools in CHO (hundred of mg or gram level)**
  - Cellca pool production package from Sartorius
  - Integration in progress (fully operational July 2022)
  - Does not include GMP production cell line development

Step 1 – PROJECT ANALYSIS

Design of a comprehensive development plan

- **Generation of mAbs**
  - Design of immunogen, including mRNA for difficult to express targets (validation in progress)
  - Generation of tools:
    - Immunogen production (soluble protein, transfectants, mRNA)
    - Screening tools (generally transfectant human mice cyno for crossreactivity)
  - Choice of animal strains : mice, KO mice for target if available to diversify epitope and allow mice crossreactivity, genetically engineered mice for direct fully human mAb obtention (Alloy GX mice)
- **Format of antibodies**
  - Full range of mice and human isotypes
  - Fc competent, ADCC enhanced Fc mutations, Fc silent mutations
  - Compare advanced formats (ADC, bispecifics)
- **Design of preclinical models**
  - KI mice (Agreement with CIPHE, 18 months to generate mice colonies for pharmacology evaluation)
  - Surrogate strategy (necessitates both human and mice immunization campaigns)
- **Generate comprehensive work program (Gantt and associated resources)**
  - Definition of go-no-go and milestones
  - Definition of reporting schedules
  - Resources are followed and adjusted depending on results/priorities

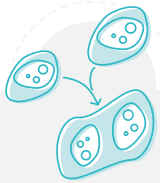
Step 2a - GENERATION OF ANTIBODIES / CURRENT PROCESS

Hybridoma technology, partially robotized

ATX-Gx Certified Service Provider

Immunization and serum screening

40 days



Fusion, hybridoma cell culture and screen (two rounds of screen)

Capacity
2000 hybrids (max 3000)

40 days

Hybridoma sequencing and pairing checking

Transient transfection and purification of leads

Capacity
up to 24 leads

20 to 40 days

18 weeks for 12 lead candidates (20 weeks for 24 leads)

Advantages

- Robust and proven record for ‘usual’ antigens

Drawbacks

- Low throughput in initial testing (2000-3000 antibodies), difficult antigens may require larger testing
- Low throughput in final selection (up to 24 lead candidates)
- Relatively long process

Step 2a - GENERATION OF ANTIBODIES / BEACON PROCESS

Introduction of Single-Cell technology and microfluidic (to be implemented in 2022)

ATX-Gx Certified Service Provider

Immunization and serum screening

40 days

BERKELEY LIGHTS

Beacon step

Beacon system and OptoSelect™ chip
Clone 10,000-40,000s of single B cells into NanoPen™ chambers
Characterize function within minutes using multiple assays

Capacity
40 000 (max 100 000 studied B cells (compared to 1500-3000 hybridoma)

7 days (instead of 60 days compared to hybridoma)

Transient transfection and purification of leads

Capacity
50 to 100 leads

25-30 days

10 weeks (instead of 20 weeks with classical method)

Advantages

- Beacon technology addresses most limitations of hybridoma technology (speed and depth of repertoire analysis)
- Speed up the achievement of mAbs against usual antigens and facilitate it for difficult ones

Step 2b – LEAD SELECTION

Functional characterization (affinity, in vitro pharmacological profiling see step 5)

Humanization of rodent mAb; In silico analysis of mAb behaviour and sequence liabilities.

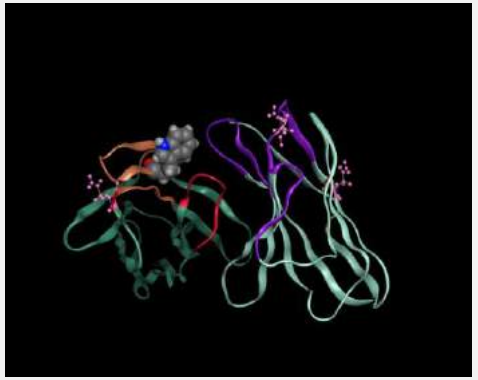
- Antibody modelling, CDR grafting
- In silico analysis of sequence liabilities on fully human or along humanization process : propose variants to decrease identified liabilities

Biochemical characterization

- Purity, integrity, aggregate content (SDS, SEC HPLC)
- Identity (Mass spectrometry)
- Endotoxin (LAL test)

Pre-CMC behaviour

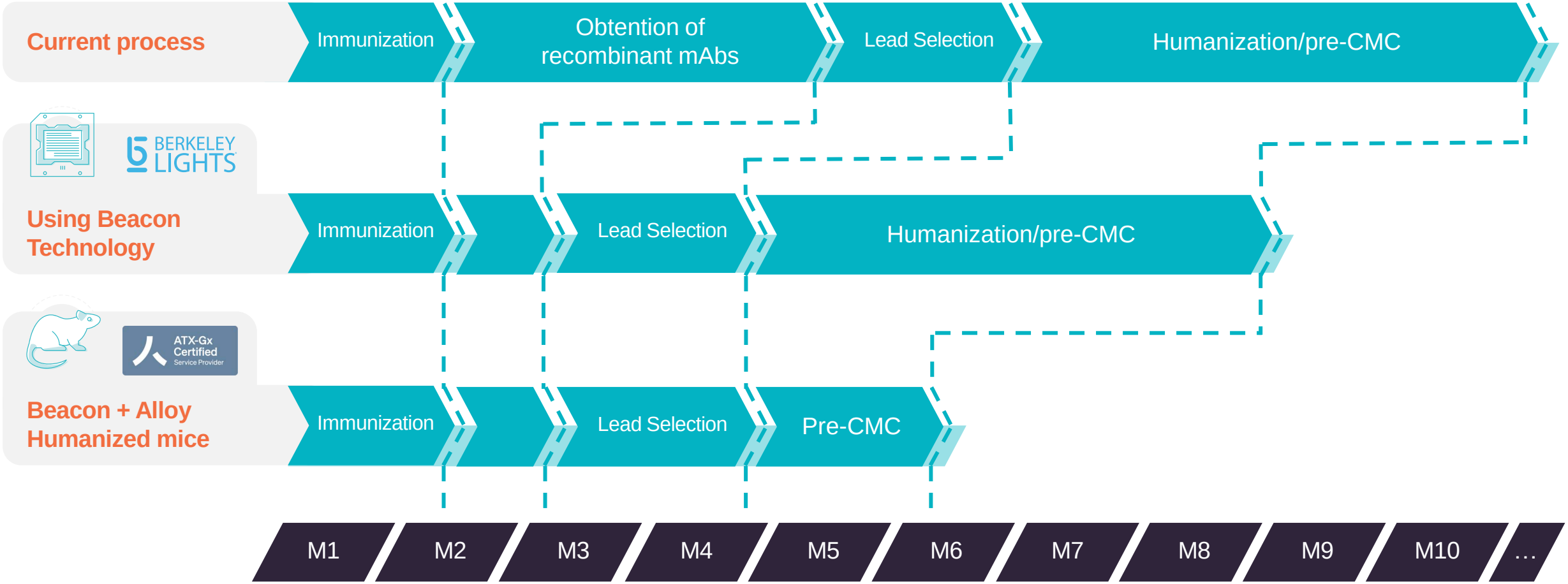
- Pre-formulation (buffer, polysorbate, sucrose)
- Accelerated stability studies of different variants (aggregation and affinity follow-up)
- Stress tests (pH, freeze thaw cycles)
- Nano-DFS and DLS studies



Modelization and analysis of sequence liabilities (N and W) of a lead candidate (MOE software)

mAbs ANTIBODIES FOR MEDICINE

LEAD SELECTION TIME



Step 3 - mAb Engineering / ADC

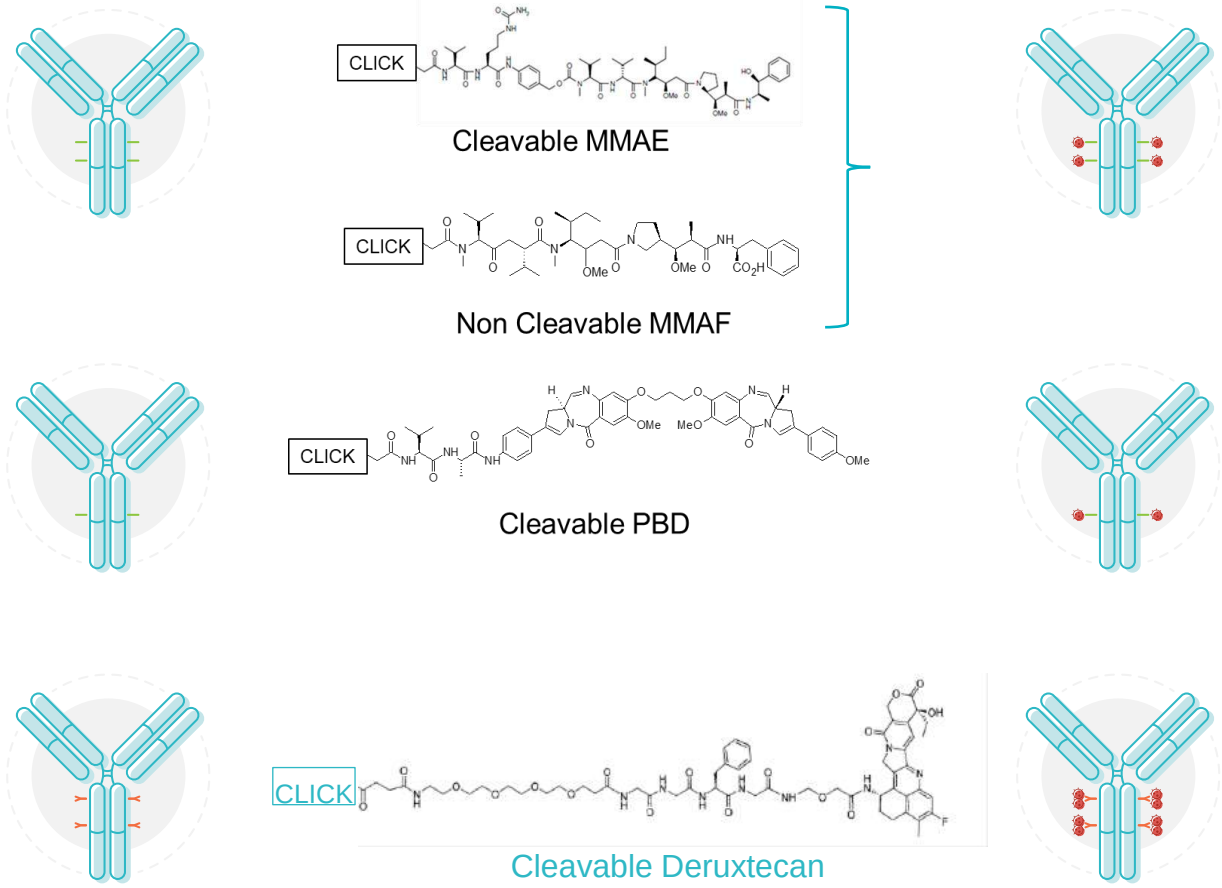
Generation of several validation packages for different candidate/toxin leading to pharma development

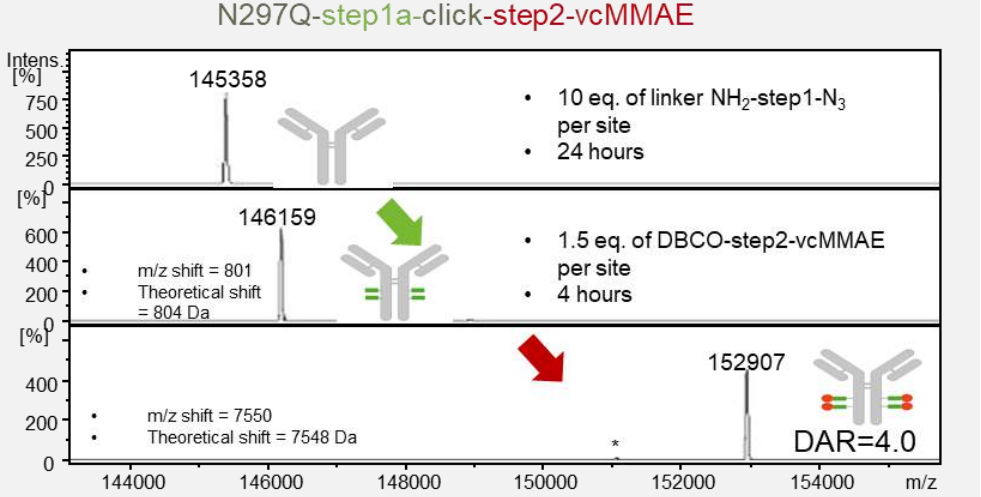
- **Generation of ADC**
  - Various technologies of coupling (random C-coupling, site directed (engineered C-coupling, enzymatic coupling))
  - Various Toxins and linker validated in the clinics (next slide)
- **Mg scale production (for in vitro and in vivo efficacy validation)**
  - Selected mAbs coupled with different toxins to evaluate differential pharmacological activity
    - Xenogeneic or syngeneic (human target transfected mouse cancer cell lines) models to evaluate efficacy
    - MTD evaluation in mice
- **Hundreds of mg scale production (for MTD determination (mice, rat) or acute toxicology in monkeys)**
  - High level quality controls, stability studies, pre-CMC packages
- **Possibility to generate KI mouse models to evaluate therapeutic window**

Step 3 - mAb Engineering / ADC (cont'd)

Toxin and DAR ratio commonly used at MImAbs

Non exhaustive list of toxins (several versions of PBD, Exatecan, linkers…)





Mass spectrometry control of a DAR 4, 2 steps, site directed MMAE ADC

Step 3 - mAb Engineering / bispecific mAb

Generation of several validation packages for different bispecific formats leading to pharma development

- **Knob in the hole/CrossmAb format (off patent)**
  - Knob in the hole mutations combined with crossmab
  - Set up of purification protocol to isolate bispecific from byproducts
- **Arm exchange format (Genmab technology)**
  - Genmab mutations and production of separated mAbs
  - Arm exchange protocol
  - Set up of purification scheme to isolate bispecific from byproducts
- **Production scale and QC compatible with pharmacology in mice (KI models) or acute toxicology in monkeys**
  - High level quality controls, determination of true bispecific format over parent antibodies or byproducts
  - hCD3e KI mice available at MImAbs (validated with blinatumomab)

Step 4 - Bioproduction

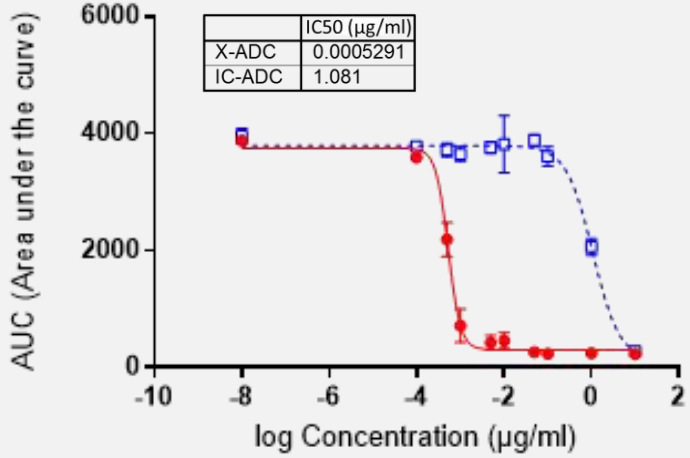
Naked , Antibody drug conjugates, bispecifics routinely produced to hundreds of mg

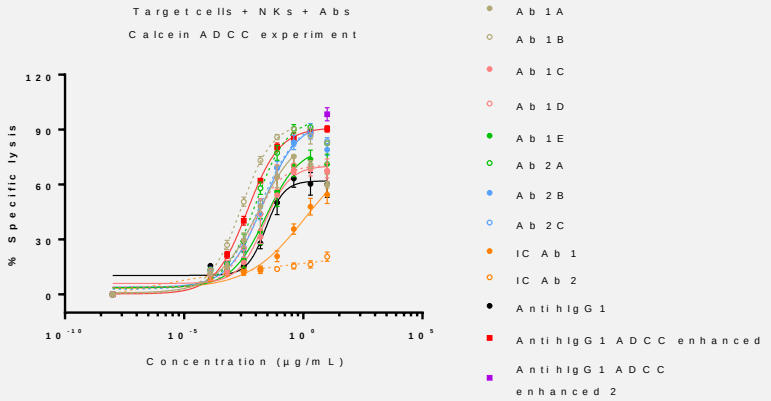
- **Mg to hundreds of mg level in transient transfection production in HEK and CHO**
  - High titer expression vectors for HEK and CHO
  - Production level compatible with in vitro and most in vivo experiments in mice
- **Gram scale level (Cellca Sartorius pool production package in progress)**
  - Stable transfection for stable pool with high productivity (100mg to gram per liter)
  - Production in Liter to 40 Liter bioreactor
  - Production level compatible with pharmacological studies in large mice experiments and non GLP non human primate (NHP) toxicology
- **Purification and Quality controls**
  - Standard protein A purification
  - Second purification step and polishing step if needed (IEX, SEC, HIC)
  - Quality controls at pharma standards for all formats (SDS, SEC, LC-MS …)
- **Batches of hundreds of mg of naked mAbs, Antibody drug conjugates are routinely produced at MImAbs**
  - Although not GMP, quality fulfill industry requirements
  - Size of batches compatible with MTD determination in mice (internally) and rats, or preliminary non GLP toxicity studies in NHP (externalized)

Step 5a - Immunopharmacology / in vitro

- **Cytotoxicity: Direct, ADCC, ADCP, CDC**
  - Direct (IncuCyte, ATP, to test ADCs)
  - Mediated by effector cells (luciferase or calcein for ADCC, T- or NK-DCC with naked or bispecific Abs)
  - Indirect flow cytometry (CD107) on effectors

- **Immune Modulation (mice and human)**
  - T cell functional assay, NK functional assay
  - Primary or secondary MLR
  - In vitro DC differentiation
  - Cytometry read-outs (surface/intra cellular stainings, cell sorting)
  - (ELISA, Luminex) read outs for cytokine production

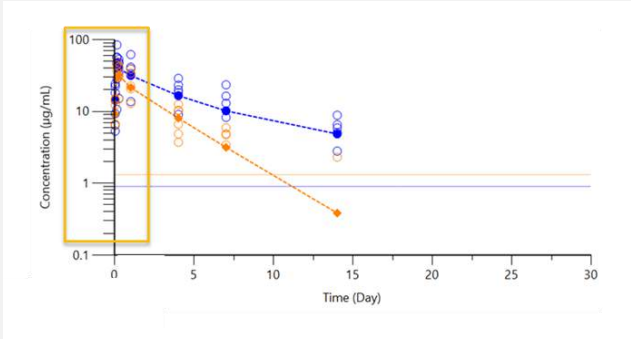


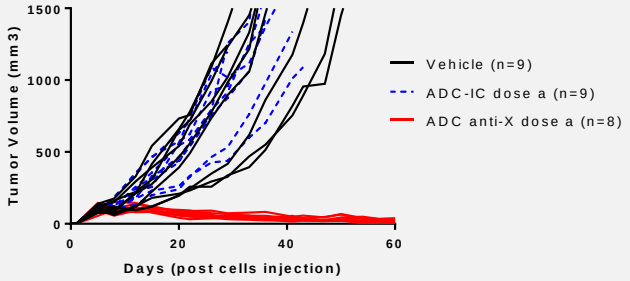


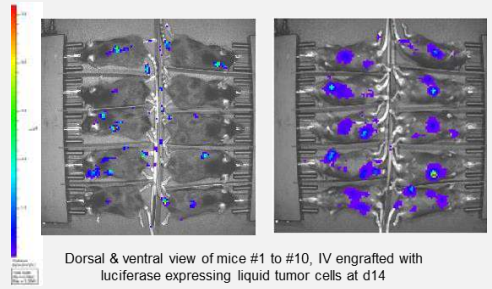
Step 5b - Immunopharmacology / in vivo (mice)

Naked , Antibody drug conjugates, bispecifics in syngenic, xenogenic or genetically engineered mice models (KI or KO mice)

- **Antibody bioanalysis**
  - PK parameters (including DAR follow up for ADC by MS)
  - Pharmacodynamy parameters (receptor saturation by flow)
- **Safety parameters**
  - Weight,
  - Health status
  - Blood counts
- **Efficacy readouts**
  - Survival
  - Tumor volume or bioluminescence,
  - Inflammatory response, tissue organisation, immune-profiling
- **Models**
  - Syngeneic models (surrogate, crossreactive mAbs) : MC38, CT26, B16, EMT6…
  - Xenogeneic models (large panel of different cell lines from different histologies
  - KI models (human target expressing mice)
  - hCD3ε KI model






Dorsal & ventral view of mice #1 to #10, IV engrafted with luciferase expressing liquid tumor cells at d14

BUSINESS MODEL

MImAbs is seeking collaborations with biotechs / pharmas / academia

Preferred Model: Full Time Equivalent (FTE)-based partnerships

- **Reserved and dedicated prioritized resources**
- Definition **of early target validation workplan** (immunogen design, specifications of mAbs (naked, ADC, bispecifics), in vitro and in vivo POC design (KI models)),
- **Generation and characterization** of a collection of antibodies
- **Antibody engineering** in different formats (naked humanized, ADC, bispecific)
- **In vivo** proof of concept in mice model

Alternative Option: fee-for-service model

- Antibody production, reformatting
- In vitro tests (ADCC, CDC, Immunopharmacology tests, custom tests…)
- In vivo tests, PK/PD, efficacy, immune profiling.

In both scenarios MImAbs does not retain any IP rights

- **All IP** generated during the service/contract agreement **belongs to Client**
- MImAbs has **no proprietary drug discovery program**

MImAbs

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