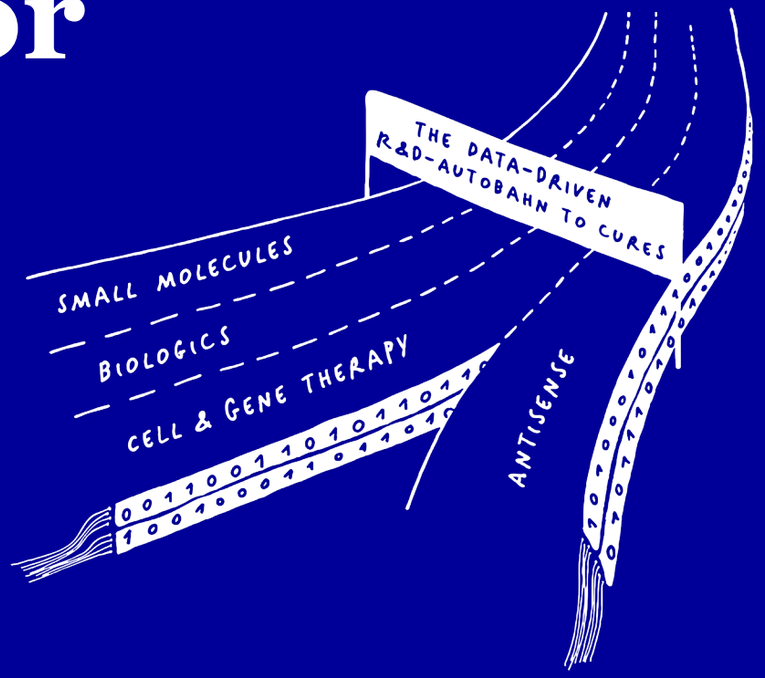
evotec

#RESEARCHNEVERSTOPS

Evotec & Just – Evotec Biologics create an “Autobahn” for Biotherapeutics

Antibody Drug Discovery and Development



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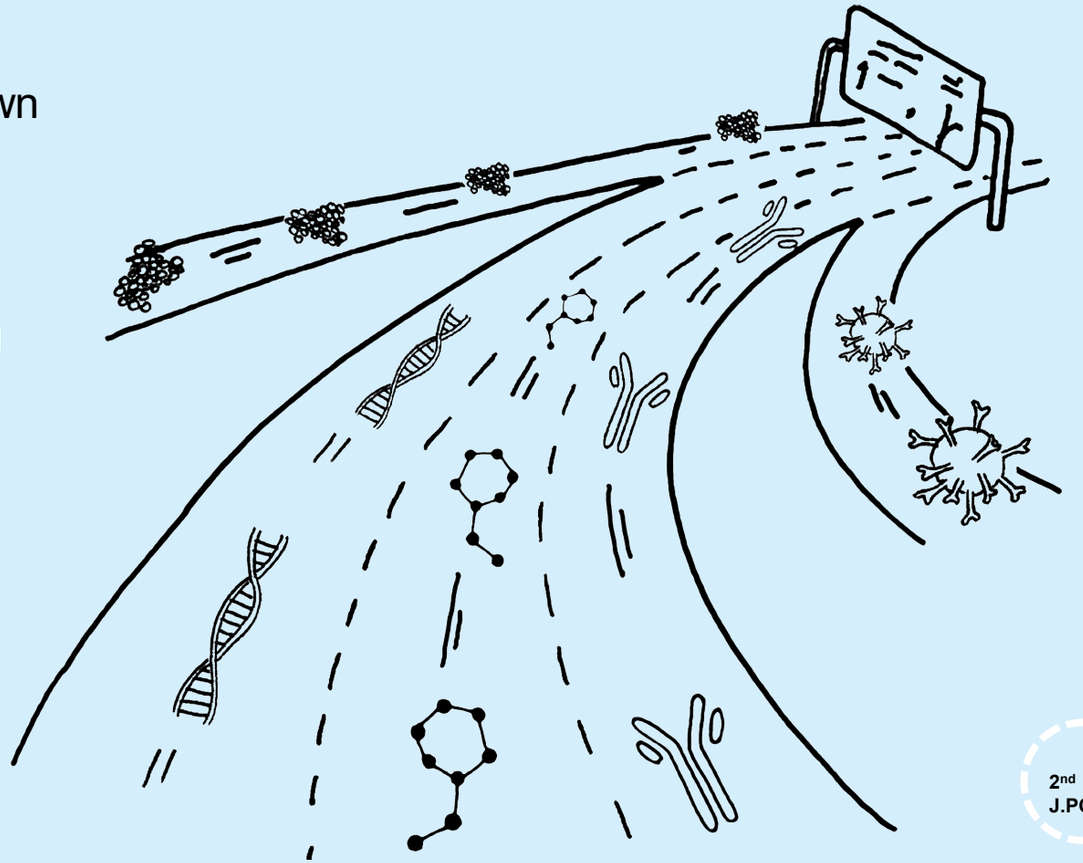
New technologies, more precision, higher speed and efficiency

Evotec footprint – 14 Sites & more than 4,000 employees

Princeton, Seattle, Branford, Watertown
~400

Orth an der Donau
~35

Verona
~700



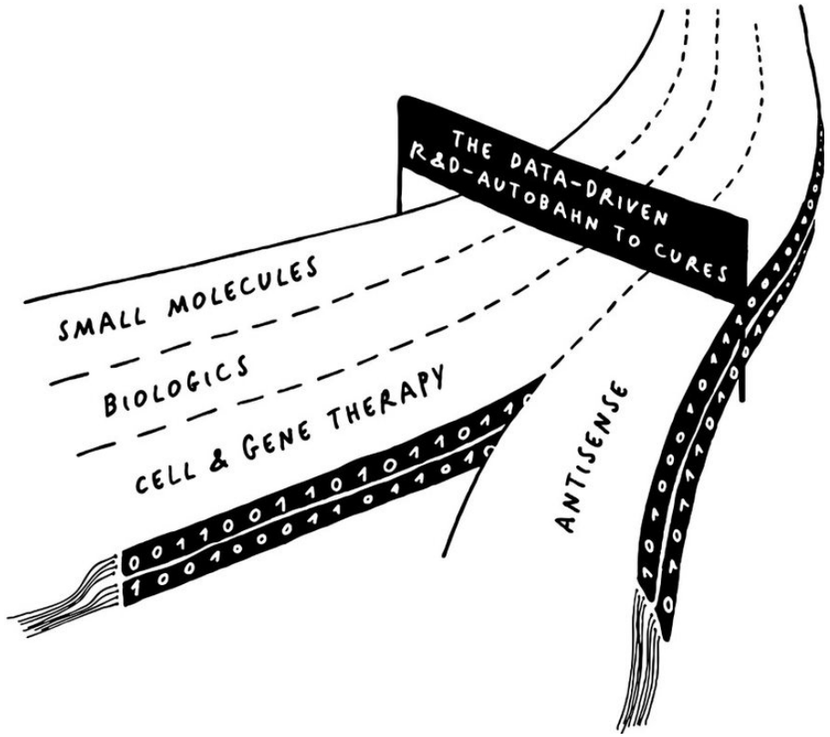
Hamburg (HQ), Goettingen (Manfred Eigen Campus) Cologne, Munich,
~900

Abingdon (Dorothy Crowfoot Hodgkin), Alderley Park
~850

Lyon, Toulouse (Campus Curie)
~800

Evotec and Just – Evotec Biologics create an “Autobahn” for Biotherapeutics

A fast road to end-to-end integrated offerings – Discovery to IND



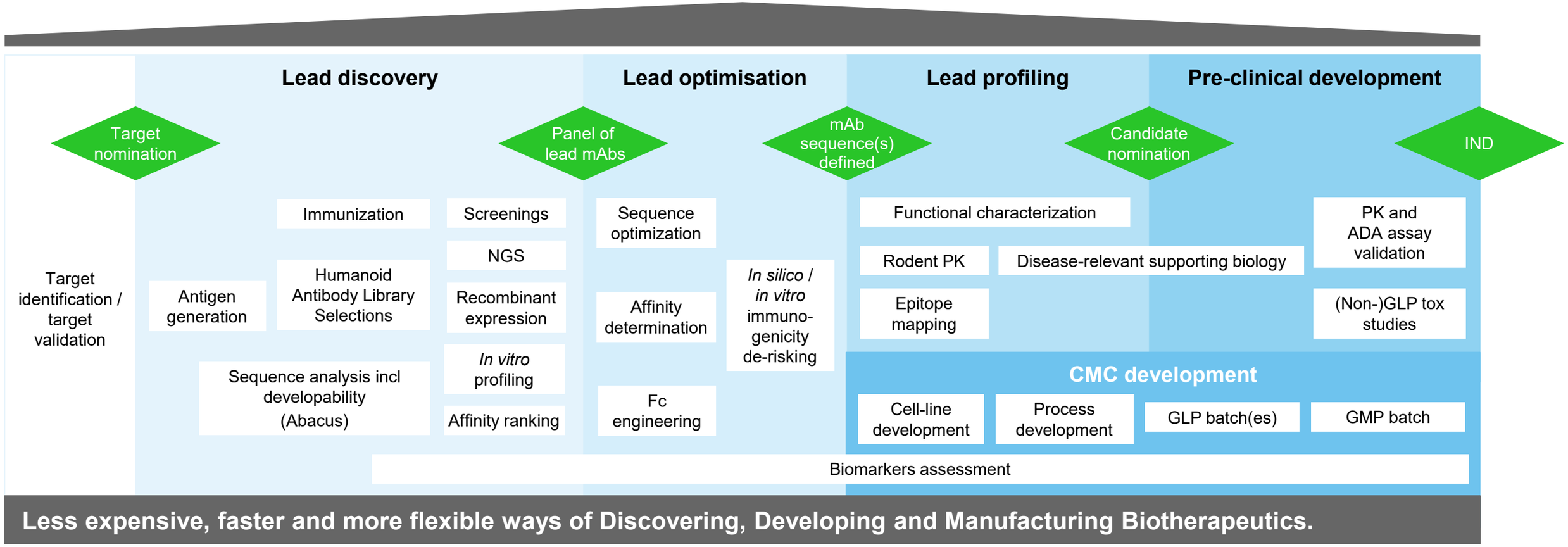
Under one roof

- The combination of the two organizations creates a powerful company with substantial capabilities from discovery to IND for biotherapeutics
- Just Biotherapeutics was founded in 2014
- Just joined Evotec in 2019, bringing deep biologics experience to an extremely strong Evotec organization
- The span of the Just – Evotec Biologics J.DESIGN design and manufacturing platform complements the significant acumen of Evotec’s early pre-clinical biology and screening, translational science, pre-clinical study design and execution

Accelerating our mission to create global access to biotherapeutics!

Unique and integrated antibody drug discovery and development

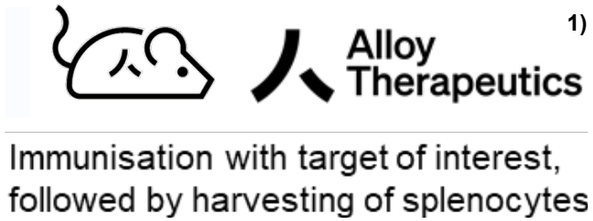
One-stop shop: From target ID to IND

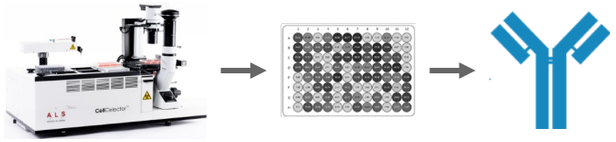


EVT antibody discovery platforms

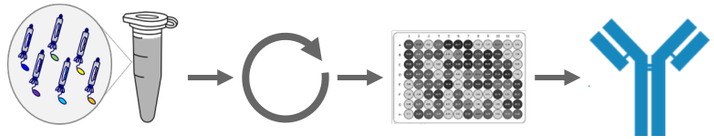
Strengthening the global Evotec offering for Ab Drug Discovery

In Vivo Antibody Production
Evolved for affinity



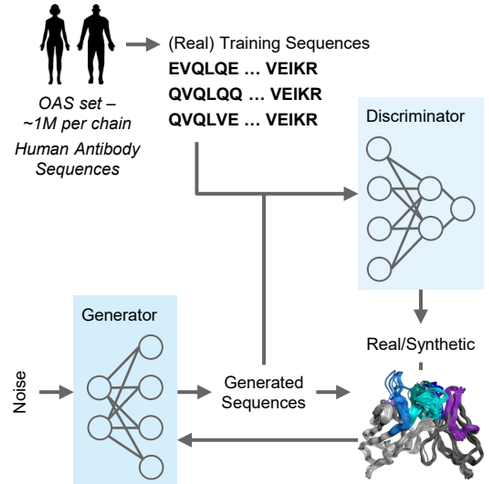


Hybridoma Technology
State-of-the-art hybridoma generation and high-throughput screening



Immune Antibody Libraries
Phage display lab in construction for the exploration of natural immune repertoires

In Vitro Antibody Production
Designed for diversity, humanness & developability



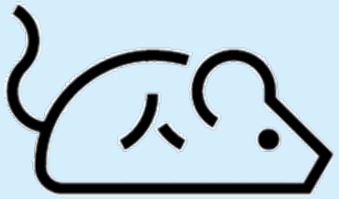
Humanoid Antibody Library (J.HAL^{SM})[2)]
Large, diverse, manufacturable & developable discovery libraries with machine-learned biasing

[1)] https://www.evotec.com/en/invest/news--announcements/p/evotec-partners-with-alloy-therapeutics-to-expand-its-antibody-discovery-platform-6010
[2)] Designing Feature-Controlled Humanoid Antibody Discovery Libraries Using Generative Adversarial Networks: https://www.biorxiv.org/content/10.1101/2020.04.12.024844v2

Best in class mAb Discovery: ATX-Gx and J.HAL

Each approach has its own advantages

Alloy Therapeutics



ATX-Gx Platform

- takes advantage of the natural *in vivo* diversification and selection mechanisms generating highly affine and specific Ab-generating B cells
- *in vivo* platforms have proven successful for clinical antibody candidates
- in clinical trials, the mAbs derived from transgenic mice outnumber those produced by phage display

J.HAL℠ HUMANOID ANTIBODY LIBRARY

J.HAL℠

- uses machine-learning to generate fully human antibodies with targeted features
- is designed to provide broad efficacy with reduced manufacturing liabilities
- provides access to hard to find or rare mAbs engaging highly diverse epitopes

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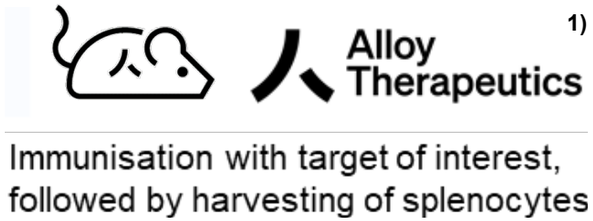

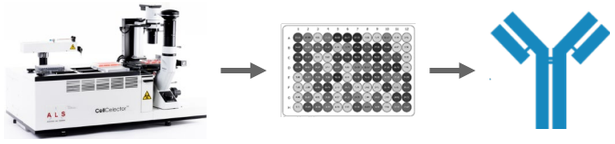

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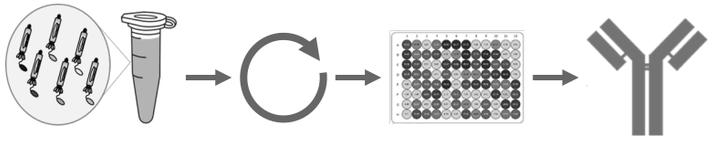

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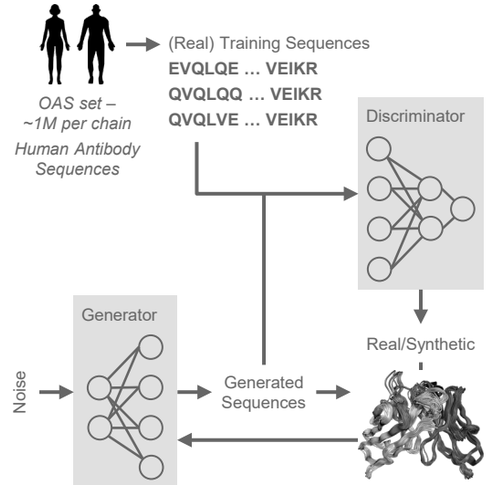

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Human Antibody Drug Discovery

Access to Alloy ATX-GK Mouse Platform for integrated discovery for Evotec‘s clients

ATX-Gx Workhorse and Precision Strains for Optimal Human Antibody Discovery

Best-in-class immunocompetence across a suite of transgenic mice

Workhorse Strains

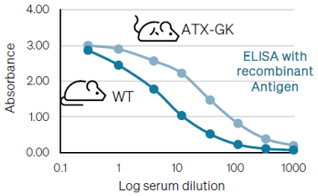
ATX-GK MIX	Comprehensive functional human Gamma heavy chain and Kappa light chain on a mix BL/6 & BALB/c background (MHC Haplotypes H-2b & H-2d)
ATX-GL	Comprehensive functional human Gamma heavy chain and 21 of 34 Lambda light chain genes on a BL/6 background (MHC Haplotype H-2b)

Rapidly expanding the platform for ATX-Gx partners

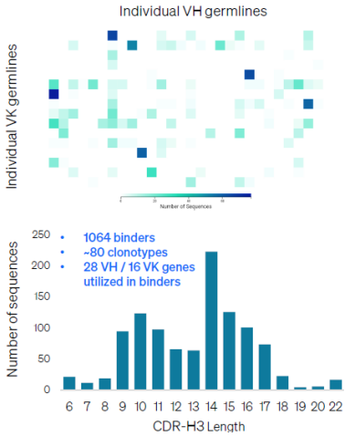
ATX-GK BL/6	Comprehensive functional human Gamma heavy chain and Kappa light chain on a BL/6 background (MHC Haplotype H-2b); available today for custom KO strains
ATX-GK BALB/c	Comprehensive functional human Gamma heavy chain and Kappa light chain on a BALB/c background (MHC Haplotype H-2d)
ATX-GK MIX	Comprehensive functional human Gamma heavy chain and Kappa light chain on a mix BL/6 & BALB/c background (MHC Haplotypes H-2b & H-2d).
ATX-pGK	First half of human Gamma heavy with full human Kappa light chains on a BL/6 background (MHC Haplotype H-2b) to limit immunodominance
ATX-dGK Q4-21	Second half of human Gamma heavy chains with full Kappa light chains on a BL/6 background (MHC Haplotype H-2b) to limit immunodominance
ATX-GL	Comprehensive functional human Gamma heavy chain and 21 of 34 Lambda light chain genes on a BL/6 background (MHC Haplotype H-2b)
ATX-HyperImmune 2022	Multiple ATX-Gx humanized transgenic lines engineered to generate human antibodies against high-homology targets

ATX-GK animals immunized with recombinant protein (ECD-HIS)

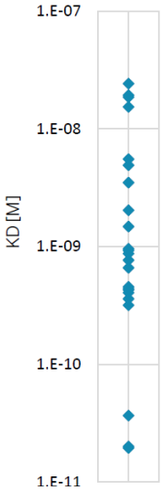
ATX-GK animals show strong seroconversion at day 21 of immunization protocol, comparable to wild-type responses



ATX-GK animals exhibit broad diversity in antibodies generated to target protein



Lead antibodies exhibit strong binding to target protein



- 24 binders produced as IgG1 and characterized
- >50% exhibit single digit and below nanomolar binding to target protein
- ~4-7 SHM per chain
- Majority of binders are cyno cross-reactive

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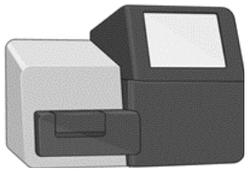
Hybridoma-based mAb generation and screening

Streamlined workflow from immunization to recombinant mAb

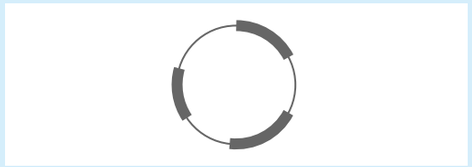


Immunizations	Hybridoma establishment	High-throughput mAb screening	Sequencing	Recombinant expression	Output: High quality panel of mAbs for functional assessment
• Customized immunization paradigms • Early screening for responder animals • Flexibility through close interaction with *in vivo* pharmacology team	• Hybridoma fusions • Cultivation of hybridomas in semi-solid medium • Automated picking of IgG-producing clones and culturing in 96-well plates • Reformatting into 384-well screening format	• Simultaneous screening for – binding to target – species cross-reactivity – off-targets • High-throughput flow cytometry, ELISA or SPR • Functional screening in cell-based assays	• NGS-based sequencing • Barcoding to define VH-VL pairs • Batch DNA synthesis, followed by cloning into mammalian IgG expression vectors	• Generation of small-scale human mAbs • Based on transient transfection of ExpiCHO cells • Analytics	• Up to 200 mAbs • <1 mg • Low endotoxin • SEC profiled • In PBS

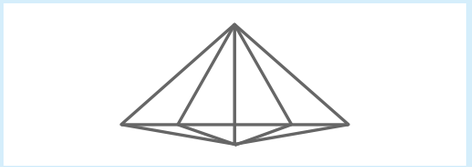
In-house production of immunization and screening reagents

Design and generation of high quality reagents

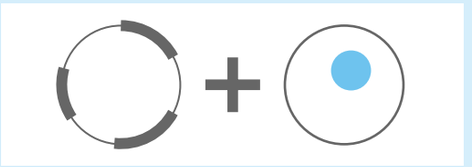
Construct design



Recombinant protein



Transient and stable cell lines



Construct design

- Literature research
- Bioinformatic tools
- Rational designs using structure biology toolbox
- Homologue and orthologue service
- Tagging and labelling strategies
- Improving cellular expression
- Improving construct stability or display

Protein production

- Expression in *E. coli*, insect and mammalian cells, and *Pichia*
- Small scale scouting to optimize expression and purification
- Construct triaging
- Scale up and purification
- QC and biophysical characterization
- Enzymatic and chemical labelling
- Endotoxin free protein for immunization and *in vivo* studies

Cell line generation

- Experience with many cell lines and primary cells
- Transient transfections
- Construct evaluations
- Selection of inducible and constitutive target expressing cell lines
- QC and functional validation of target activity
- Large scale production of transient or stable cell lines
- Large scale frozen cell batches

On-site immunization by Evotec's *in vivo* pharmacology team

State-of-the-art animal facilities to support antibody generation

Evotec Hamburg

- **Area:** 10,000 sft; conventional & barrier animal facility
- **Mouse/rat**
- **Co-located with *hybridoma group*, *Biophysics***
- ***In vivo* staff: 25**

AAALAC accredited

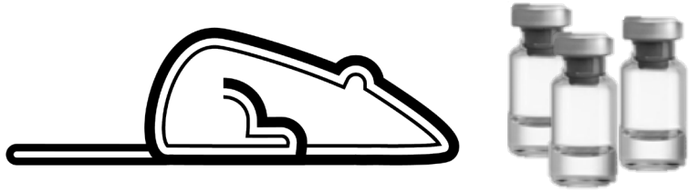
Evotec Toulouse

- **Area:** 17,200 sft, conventional animal facility
- **Mouse/rat/rabbit**
- **Co-located with hybridoma group, protein science, Biophysics, DMPK**
- ***In vivo* staff: 80**

AAALAC accredited

The capabilities

- Customized immunization paradigms using recombinant proteins, peptides and/or live cells
- Immunization of wildtype and/or tolerance-compromized strains for hybridoma workflow
- Transgenic mice for generation of fully human antibodies

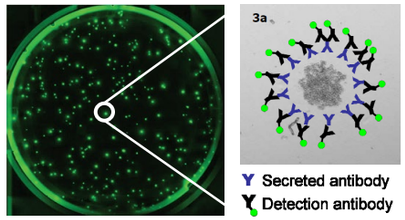


State-of-the-art hybridoma generation and cell-based high-throughput screening

Allows for rapid lead identification

Semi-solid medium-based hybridoma generation combined with automated clone picking

- Hybridoma clone picking performed by automated CellCelector™ device that can discriminate antibody producing from non-producing hybridoma colonies
- Automated transfer of monoclonal cultures into 96-well plate format facilitates culturing and screening of large numbers of hybridoma
- Eliminates the need for time-consuming sub cloning of potentially oligo clonal cultures



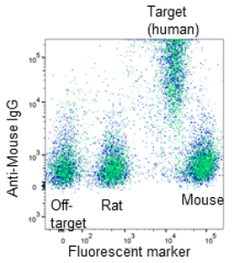
Selection of monoclonal, producing clones from the beginning

High-throughput screening of hybridoma clones on various cell populations simultaneously

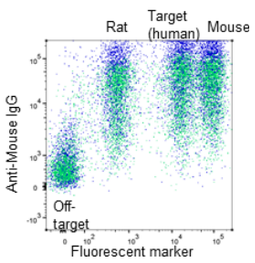
- iQue3 screening flow cytometer in combination with multiplexing approach allows early assess-ment of binding to
  - **Counter targets** or family members
  - **Tox species** (rat/cynomologus macaque) or
  - **Primary target cells** expressing native target

Intellicyt iQue3:
13 parameters (3 lasers)
High-throughput
Flow cytometer

Human only clone



Rodent X-reactive clone

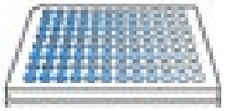


Gain essential information as early as possible

SPR-based affinity screening

Biophysics to support the selection of lead candidates

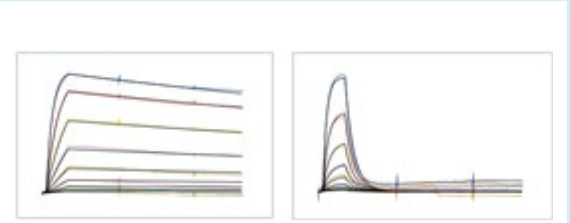
Supernatants from cell cultures



Ranking of antibodies

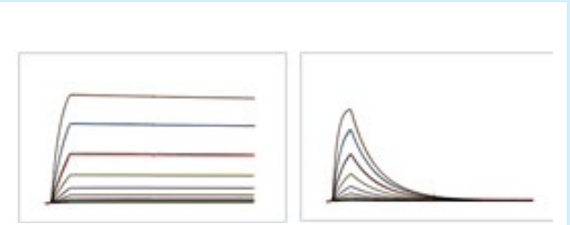
Upscale of most interesting Abs & purification

Full kinetic analysis incl. controls



Lead optimization

Full kinetic analysis incl. controls



4x T200 and 3x 8k/8k+ SPR devices from Cytiva are available at Evotec group

- SPR-based screening of Abs from cell supernatant or µscale production
  - Screening of all antibodies at a single dilution of cell culture supernatant
  - Validation of top hits with increased cycle times
- Full kinetic analysis of upscaled and purified antibodies
- Automated processes including testing and data analysis
- Off-target and cross-reactivity screening: binding of antibody to different antigens (mutants, expression host, related classes)

Assessment of binding and characterization of MoA/selectivity

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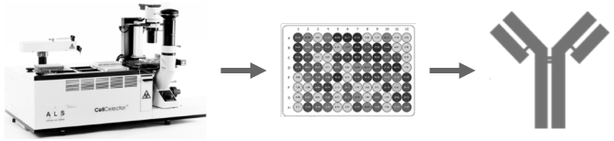
Alloy Therapeutics [1)]

Immunisation with target of interest, followed by harvesting of splenocytes



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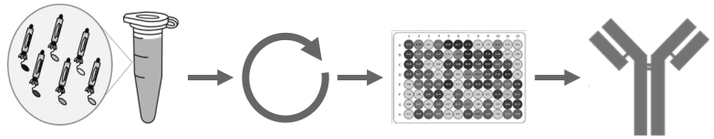

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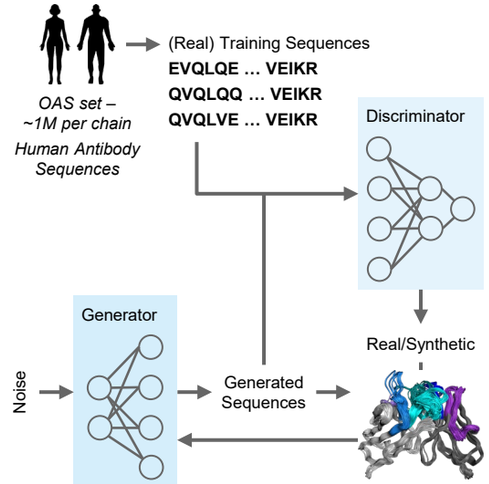

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Systems approach creates continuous learning from data

Integrating molecular, process and manufacturing design delivers excellence

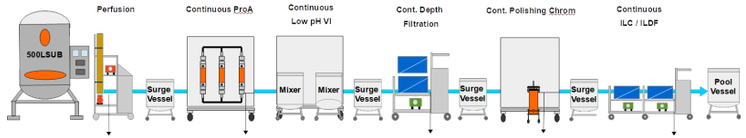
in vitro

J.HAL℠

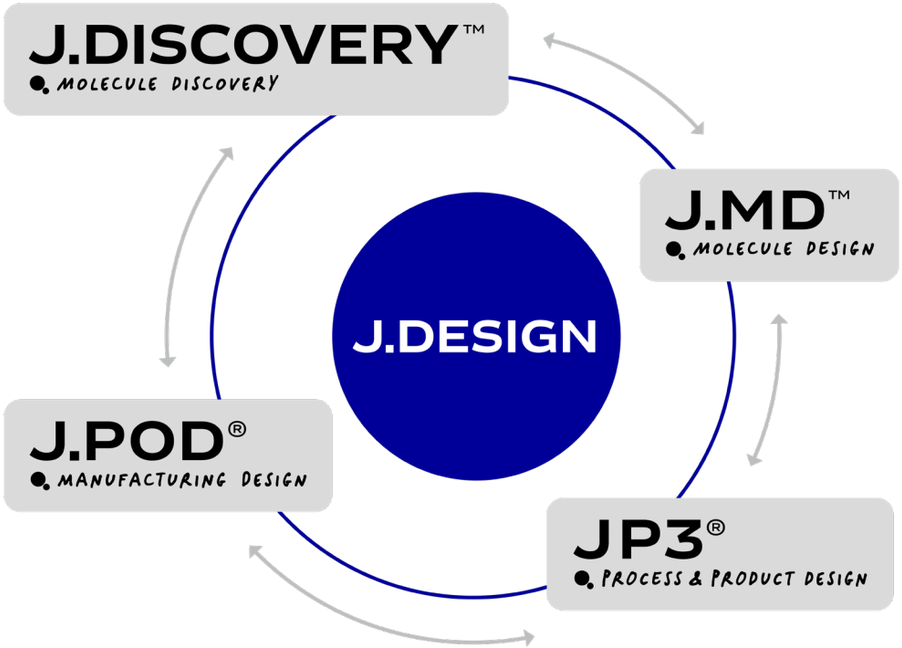
AI DESIGNED mAB LIBRARY

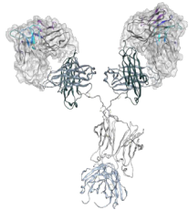
in vivo

AI generated and *in vivo* discovery

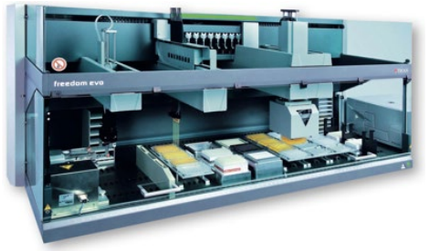


End-to-end continuous processing (E2E)

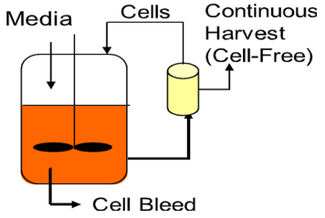




Abacus optimization to fit process development



Robotic high-throughput process development



Dynamic predictive process control

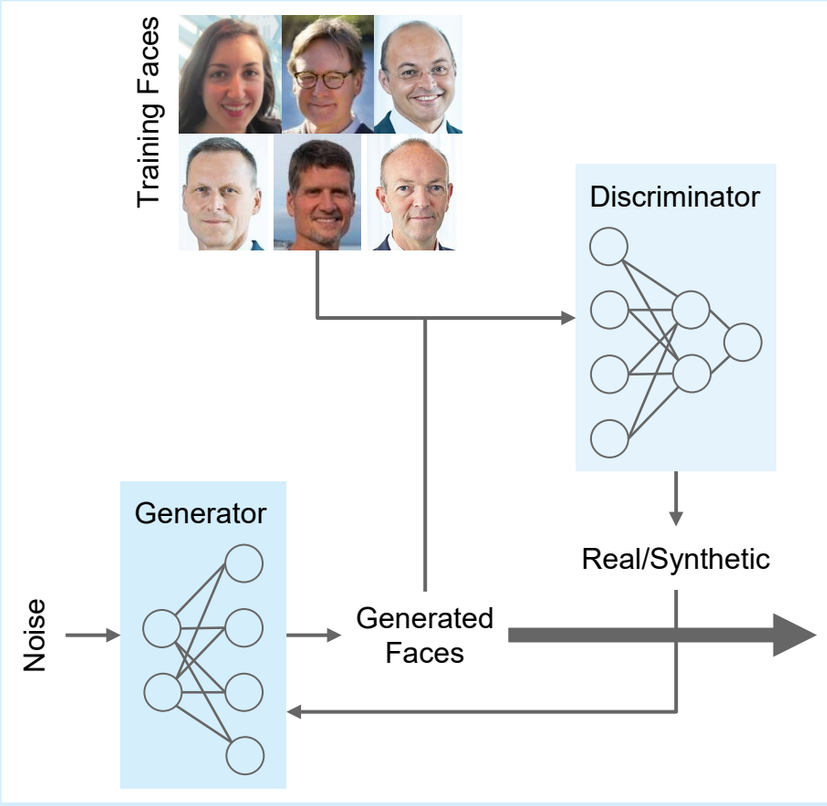
Machine learning (ML) and Artificial intelligence (AI) are maturing our integrated biologics platform (J.DESIGN)

J.HAL^{SM} utilizes Generative Adversarial Networks (GAN) to create synthetic realistic outcomes

GAN generators output results trained to fool a trained discriminator

Using human faces as an example

- Lightly train a Discriminator neural network on real human faces
- A generator begins generating images that sometimes fools the discriminator, and slowly learns to better fool the discriminator
- Continue training the discriminator with real human faces, forcing the generator to improve
- Eventually the generator can fool both discriminator and humans

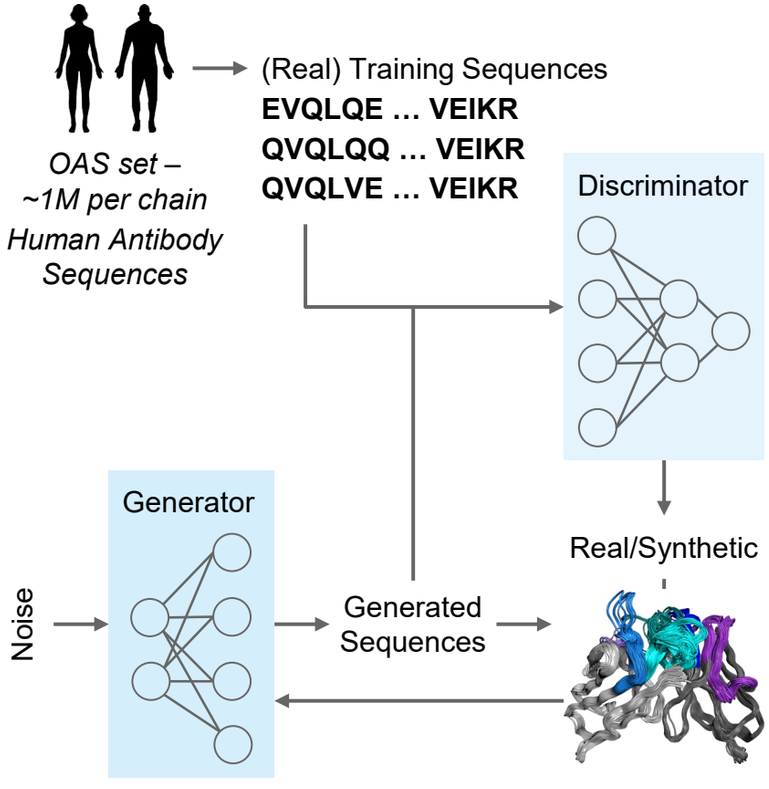


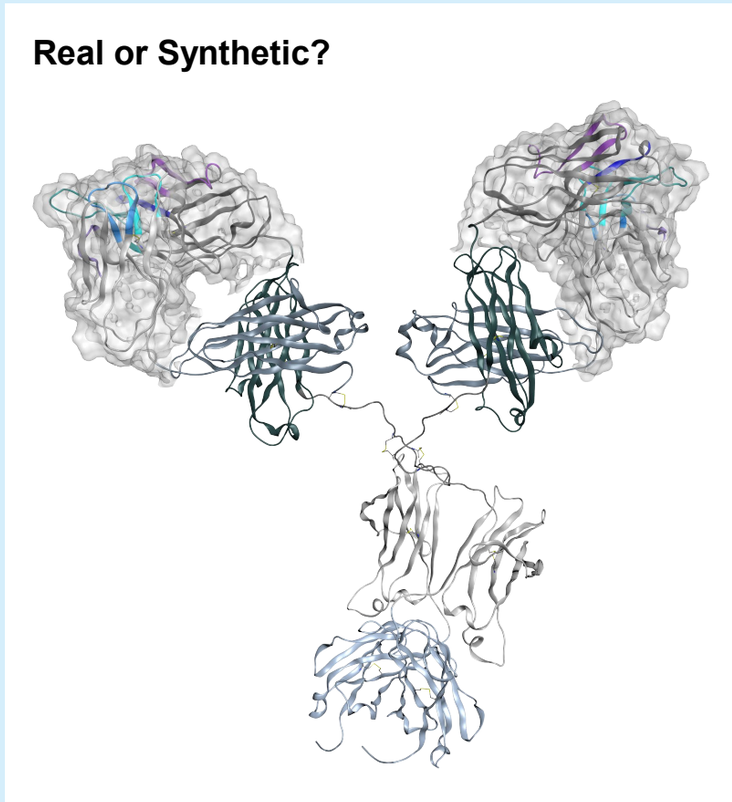
Real or Synthetic?

J.HAL^{SM} technology is a GAN application for antibody sequences

Trained on **real** mature human antibody sequences

- Large, human-derived antibody sequence training set extracted from OAS
- Abacus™ is used to clean, analyze, classify, and place sequences into structure positions
- GAN training models are germline specific
- Ability to generate synthetic humanoid large, diverse, combinatorial germline pairings for library creation
- Preprint available at bioRxiv (https://www.biorxiv.org/content/10.1101/2020.04.12.024844v2)



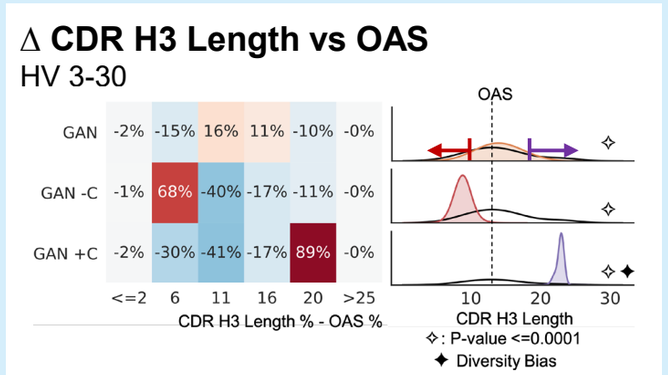


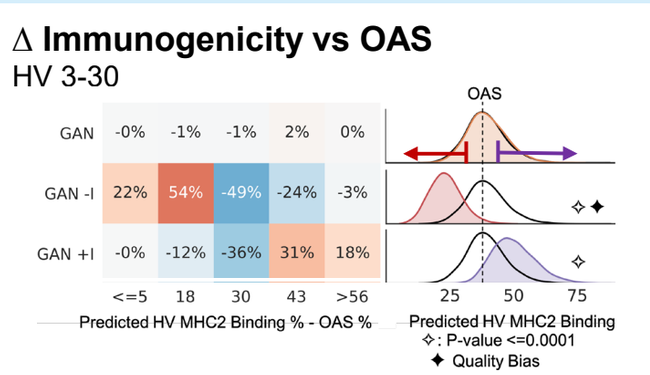
OAS paper: Kovaltsuk, A., Leem, J. et al (2018). J. Immunol. 201. 2502-2509

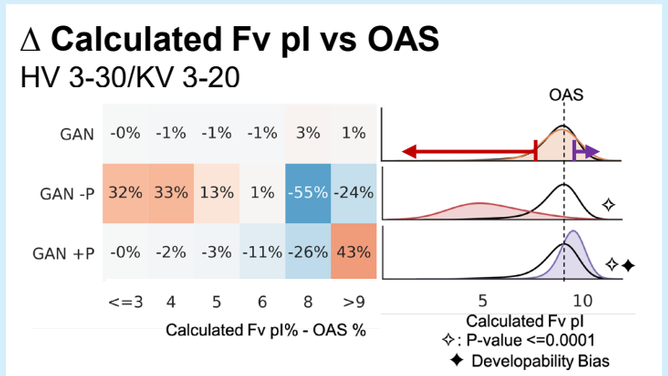
GANs control design through transfer learning

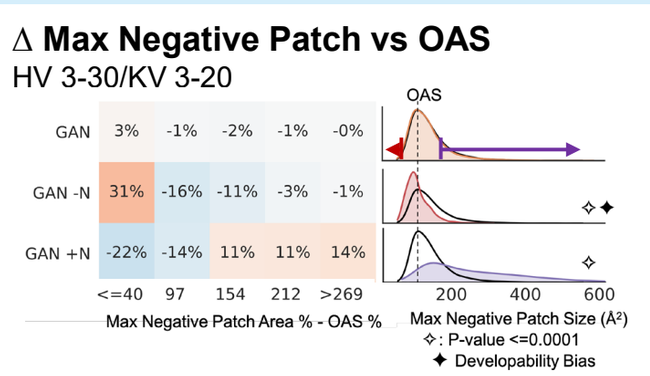
This allows us to focus the generator on specifically desired properties

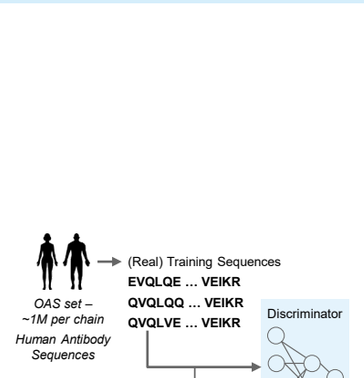
- Properties are transfer learned by further training the existing GAN with sequences which exhibit the desired property
- The mechanism of the property could be known or unknown
- A known mechanism could be CDR length, charge, pI, predicted immunogenicity, etc.
- An unknown mechanism could be temperature or pH stability, long pharmacokinetics, etc.
- J.HAL[SM] under continuous development and growth





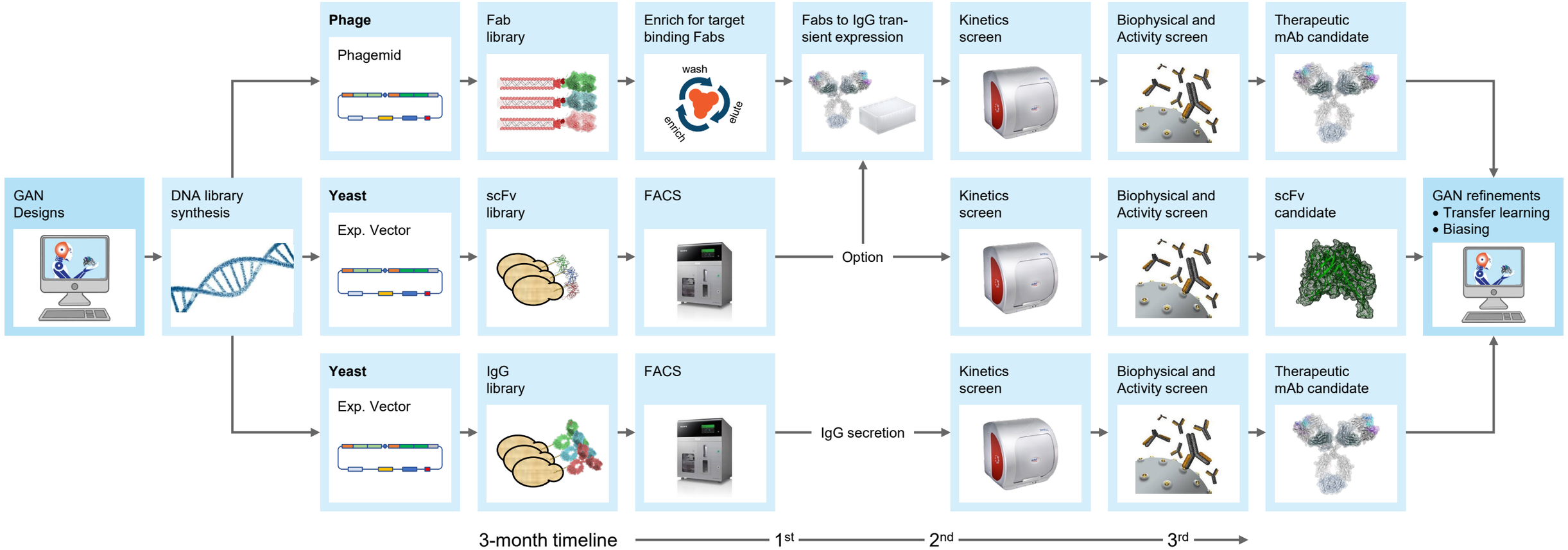






Antibody display library screening workflows

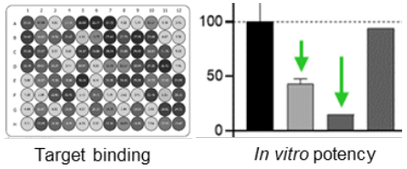
DNA sequencing is performed at most steps for panel identification



We don’t just make Antibodies, we make Therapeutics

Typical workflow for a soluble antigen

In Vitro
Hit identification
Specific binding
(incl. cyno/mouse/rat)
Functional *in vitro* profiling



In silico
Abacus™

Alloy Therapeutics

J.HAL℠ HUMANOID ANTIBODY LIBRARY

Antigen design considering desired binding site

Immunization

Panning / Screening

Hybridoma or immune library / Screening / Sequencing

Affinity maturation / Screening

Expression / Purification followed by affinity ranking

Developability assessment using Abacus

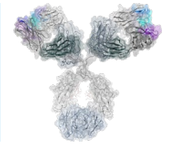
Leads: Functional testing in stably transfected *in vitro* assay(s)

Molecular Optimization

In Vivo
Disease model(s)
Rodent PK

Ex Vivo
Disease-relevant
functional assay(s)

Functionally active, fully human and developable PDC

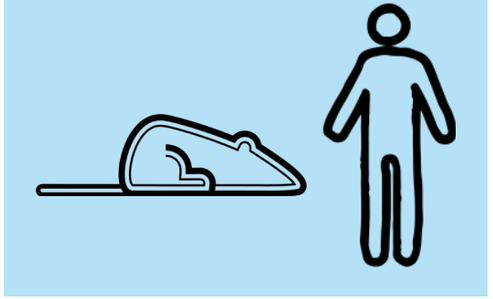


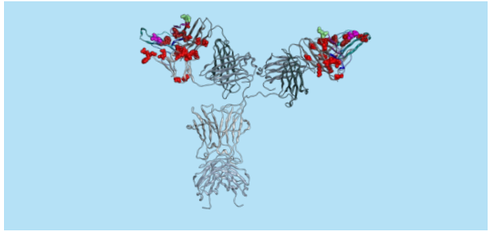
J.MD™ MOLECULE DESIGN

Partner or client antibodies from animals or people are improved for manufacturing and formulation

Abacus – an *in silico* computational toolset of ML algorithms

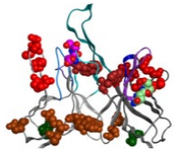
J.DISCOVERY™ MOLECULE DISCOVERY — J.MD™ MOLECULE DESIGN — JP3® PROCESS & PRODUCT DESIGN — J.POD® MANUFACTURING DESIGN





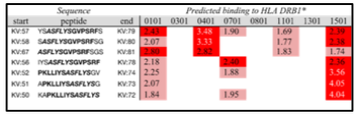
Abacus

Antibody Fv with hot spots displayed

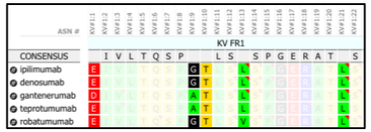


Germline Switching

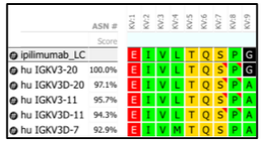
ML Immunogenecity Predictor



Structure-based alignments



Germline Analysis



Hot spot tables

Molecules optimised for

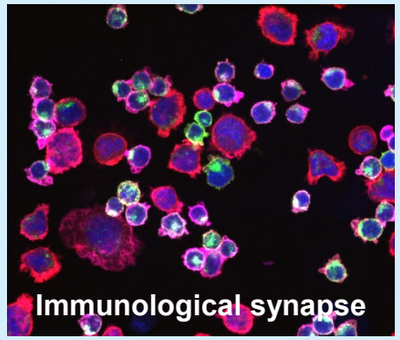
- Titer
- Purification
- Formulation
- Long-term stability
- PK
- Immunogenicity

Molecular optimisation builds in quality

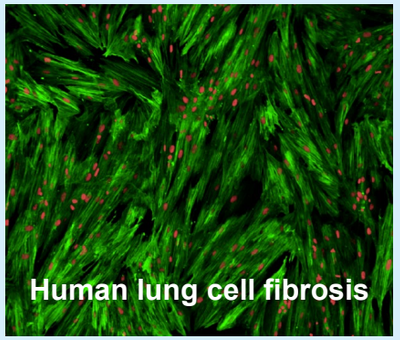
Lead antibody profiling with translational approaches

Broad range of therapeutic area expertise facilitates set up of disease-relevant biological assays

Access translational platforms early in the discovery process to predict downstream *in vivo* efficacy and demonstrate target engagement



Combined with physiologically relevant readouts through innovative technologies



Multiple rare diseases

Tuber-culosis

Liver disease

Infectious diseases

CNS

Autoimmune disease

Kidney diseases

Fibrosis

Multiple cancers

Inflammation

Womens' Health

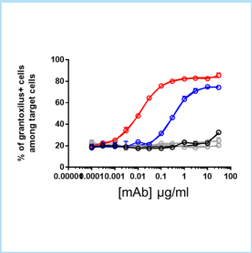
...

Isolation, cultivation & manipulation of primary cells

- **Brain/PNS:** CNS-derived neurons, DRGs, moto-neurons, astrocytes, microglia including co-cultures
- **Blood:** PBMCs, T or B cells, monocytes, neutrophils, dendritic cells
- **Pancreas:** islets, beta cells
- **Kidney:** podocytes, glomeruli, mesangial cells, PTECs, fibroblasts
- **Muscle:** myoblasts, myotubes, cardiomyocytes
- **Lung:** bronchial epithelial cells, lung fibroblasts
- **Others:** adipocytes, patient tumours
- **iPSC** derived from patient fibroblasts or PBMCs
- …

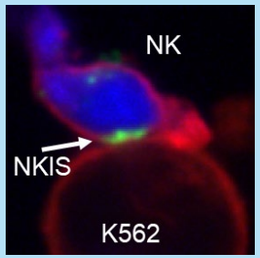
Lead antibody profiling with translational approaches

From triaging to building a strong data package for the clinical candidate



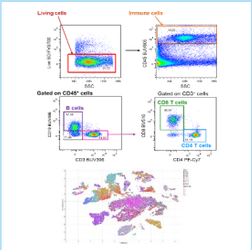
Functional *in vitro* Immunological assays with primary immune cells

- 96w or 384w plate formats
- Proliferation, cytokines production, killing, tracking of surface markers, suppression assay



Visualizing Immune cells "in action" at the contact of tumor cells or APC

- Immunological Synapse
- Analysis of antibody-mediated modulation of the immune cell signaling



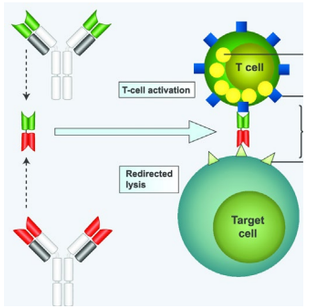
Filling the gap in drug discovery by accessing fresh patient samples

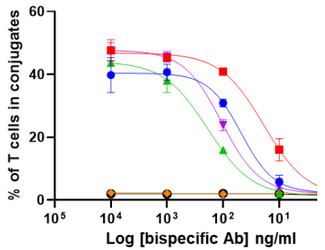
- FACS on fresh human tumor resections
- **Biomarkers for the clinic:**
  - Whole blood functional assay
  - scRNAseq, proteomics, metabolomics, etc.

INSTITUT UNIVERSITAIRE DU CANCER DE TOULOUSE Oncopole

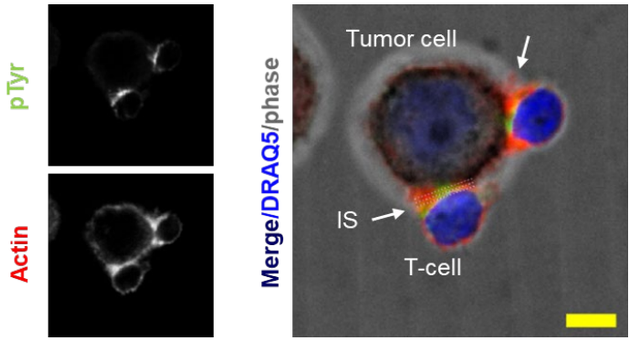
Hôpitaux de Toulouse

Case study: evaluation of bispecific antibodies





T-cell activation with bispecific Abs



Note: IS (Immunological Synapse), CTL (Cytotoxic T Lymphocytes)
Source: scheme from Baeuerle PA and Reinhardt Cancer Research 2009

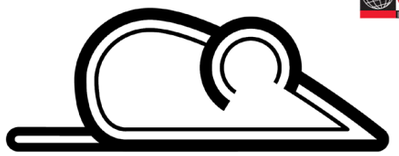
Comprehensive offering to support translational biology

PK and PK/PD characterization of Biologics

- Solid track record for successful application of PK and PK/PD strategies in different therapeutic areas
- Numerous scientists with accumulated experience to implement *in vivo* PK and PK/PD translational studies from target validation to development phases

In life phase

- Rodents, including mice expressing the humanized form of the target or humanized FcRn mice & NHPs
- Available range of existing animal models in different therapeutic areas
- Development of novel animal models

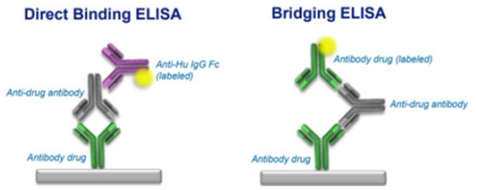


Biomarker assay

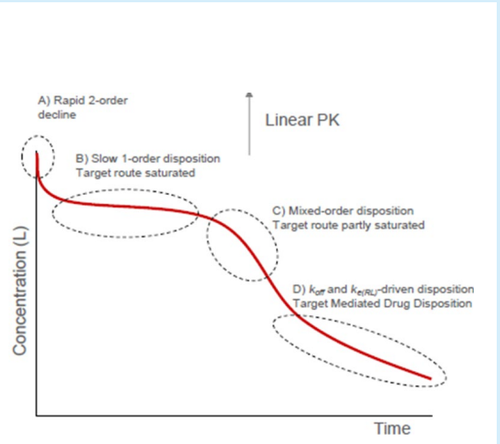
Large number of biomarkers linked to mechanism of action in addition to the efficacy end points in disease models

Bioanalysis

Unique bioanalytical platform, including ligand binding assays and LC/MC-MS, available to support *in vivo* PK & PK/PD Studies



PK, PK/PD Modeling

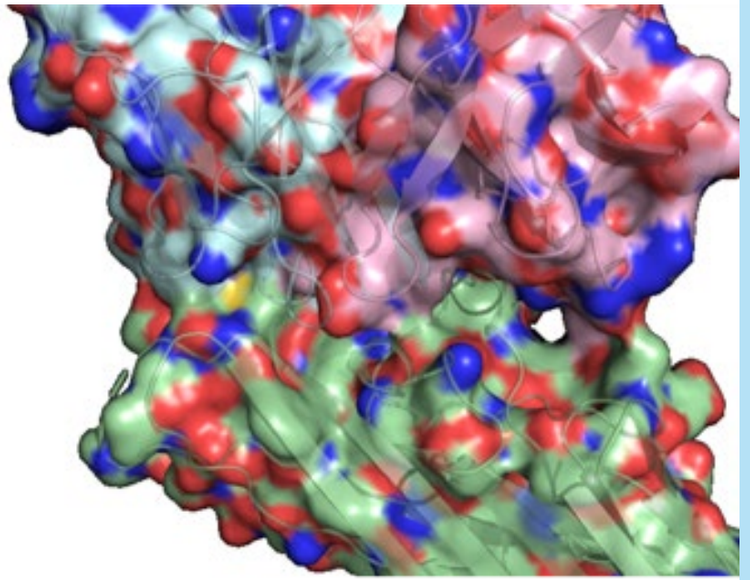


Lead antibody profiling to assess relevant epitopes

Multiple platforms for epitope mapping available

Multiple platforms available to define and secure the IP of the mAB antigen binding epitope

- Competition experiments on assay platforms
- Linear peptide or receptor chimera binding
- Cryo-EM
  - Negative stain or single particle cryo-EM of the antigen and full length mAB complex
- X-ray crystallography
  - High resolution typically via FAB (or FAB') complex with antigen
- NMR
  - Antibody binding to labeled protein target provides info about epitope
- Hydrogen Deuterium Exchange (HDX-MS)
- SPR
  - Epitope binning



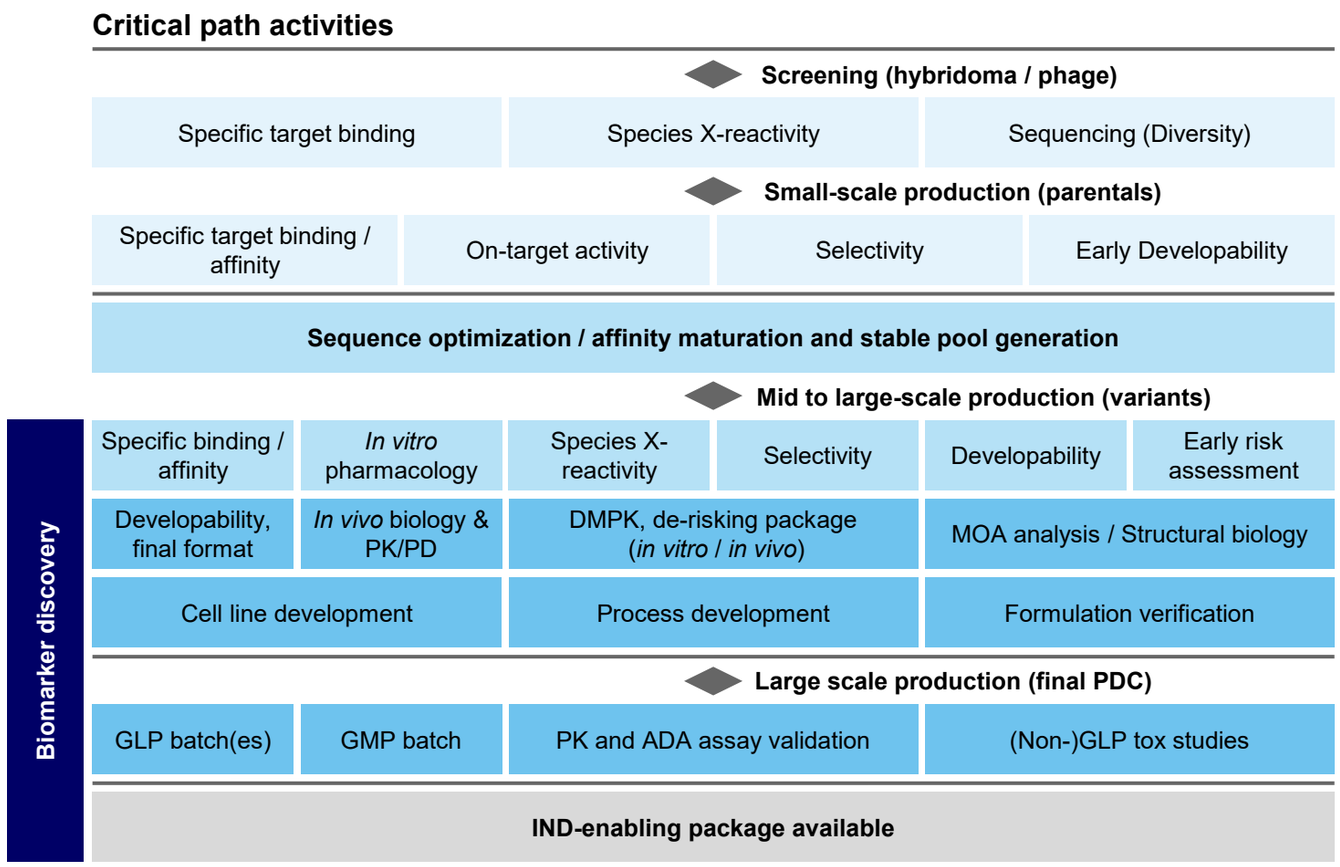
100's in competition experiments

10's of epitopes binned in negative stain or HDX

Individual complexes at Atomic Resolution

A powerful integrated platform for biologics …

Evotec's Hit-to-Candidate Screening Philosophy



- Screening of ~10^3-10^4 clones
- VH/VL sequence information to inform about diversity
- Small-scale expression of up to 200 unique mAbs including early developability ranking
- Initial profiling of mAbs (confirmation of binding and selectivity, focus on: functional active vs. binder only assessment)
- Assessment of sequence liabilities

▲ **Selection of 1-2 lead candidates for sequence optimization**

- Confirm binding, affinities, specificity and functional activity after engineering
- Extended developability assessment
- Large scale expression of promising candidates for *in vivo* testing
- De-risking package to inform about safety etc.
- In-depth understanding of MOA, differentiation potential, targeted epitopes
- Biomarker discovery to support clinical development

▲ **PDC nomination**

- Product generation: confirm that it is safe, effective and consistent between batches

Lead Discovery | Lead Optimisation and Profiling | CMC and Pre-clinical development | Clinical development

Seamless integration from idea to IND and beyond

World-class drug discovery & development, INDiGO and high-end CMC

PDC

Best-in-class Drug Discovery
- Integrated solutions across with full suite of multidisciplinary capabilities for TV and Hit finding
- Expertise in multiple therapeutic areas: CNS, fibrosis, oncology, anti-infectives, metabolics, inflammation …

Preclinical studies and INDiGO
- Seamless transition from development candidate through to pre-clinic and IND

Small molecules high-end CMC
- GMP manufacturing for clinical development programmes and Niche scale commercial API and Drug Product

Biologics Molecule Optimization – J.MD™
- ML based sequence evaluation for lead selection of best molecules for rapid and efficient manufacturability and formulation stability

Biologics process development – JP3®
- Formulation design from clinical to commercial with powerful analytical, ML and high-throughput tools

Biologics high-end CMC – J.POD®[1)]
- Modular and flexible clinical and commercial manufacturing at highest quality and low costs
- Seamless integration

[1)] J.POD is currently under construction – expected early 2021

Preclinical Safety

More than 100 scientific experts dedicated to preclinical safety

Research Discovery | **Phase I** | **Phase II** | **Phase III** | **File & Launch** | **Lifecycle Management**

Exploratory & Regulatory Safety

- **Integration** with **Bioanalysis, PK/PD, Toxicokinetics, CMC**
- **Immunogenicity assessment**
- **General Toxicology** studies in rodent, dog & NHP
- **Tissue Cross Reactivity** and **species selection / strategy**
- **IHC** expertise
- **Biodistribution** assessment with detection methods including radio-, LC-MS, qPCR
- **Genetic Toxicology**
- Strong expertise in **Safety Pharmacology** (endpoints can be included within general toxicology studies as appropriate)

Broad interventional experience with Biologicals including:

- **mAbs**
- **Vaccines**
- **NBEs**
- **Peptides**
- **Viral vector/gene therapy**
- **Cell therapy**

A Further Array of Fit-For Purpose Technologies

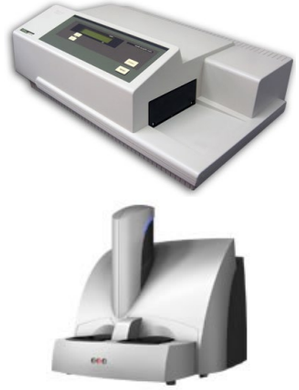
Analysis & Assessment (supporting mAb development)

LC-MS/MS

- Q-TOF experiment for peptide selection supported "*in silico*" digestion
- Quantification of 1 (or more) signature peptide obtained by tryptic digestion of the mAb
- Use of commercial kits for sample preparation
- Generic SILs available on market
- Determination of the mAb total content
- Sample prep supported by robotic liquid handlers
- Reproducible and robust methods (longer analysis)

LBA

- 96-well plate based: CS & QC in each plate, samples
- Assayed in duplicate wells
- General Human IgG assays commercially available (preclinical matrices)
- Critical reagents needed for proprietary assays
- Total & Free mAb quantification depending on assay format and critical reagents



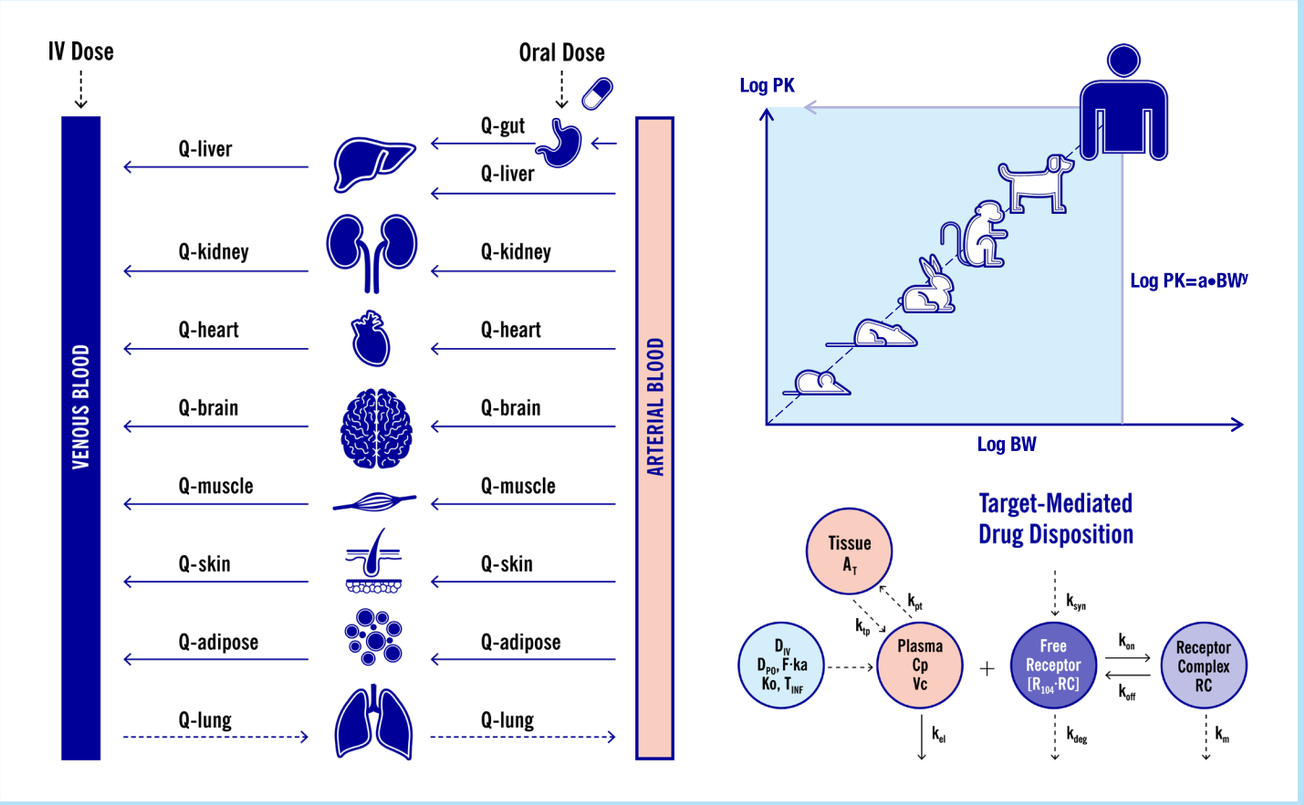
TEM

- Used to demonstrate Immunocomplex deposition
- Technical & interpretative TEM expertise in-house
- TCR

PK/PD Continuum Transitioning from Discovery throughout Development and within the Clinic

Characterisation, assessment and model selection

- Target (and MoA) driven tailored approach
  - Cellular vs. soluble, density, affinity, turnover
  - Antagonsim, agonism, cytotoxicity
  - Fc activity
- Species / *in vivo* model choice
  - Knock-out/in
  - Surrogate molecule for test species
- PK and PD model fitting
  - Automated fitting to bank of models as first approach
  - GOF driven selection
  - Iterative, data driven process from selection through preclinical to clinical development
  - TMDD, functional bioassay data-based adaptations
  - PBPK approach as data / information allows



De-risking your mAb

Topics for evaluation of developability

Discovery (internal or external)	De-risking	Pre-clinical development
• mAb identified	• Molecular optimisation • Stable pool and process development • Purification strategy • Formulation development	• Cell line & upstream development • mAb Production • Drug Product supply
	• Selection & Justification of tox species – Target sequence assessment – Binding assay(s) – Tissue cross reactivity – Pharmacokinetic profiles (BA method dev) • Immunogenicity assessment *in vitro*	• ADA assay development • DCA method transfer/development • Non GLP and GLP toxicology studies • Non GLP PK-PD
	• *Preliminary non-GLP in vivo safety evaluation* • *Early prediction of effective dose*	• *GLP Human TCR*
	Translation, PK & PK/PD Modelling & Simulation	

Propriety reagents and methods, coupled to robotics & ML can rapidly move client or partner molecules into the clinic

Highly efficient process and product design delivers high quality, low-cost therapeutics

J.DISCOVERY™ MOLECULE DISCOVERY — J.MD™ MOLECULE DESIGN — JP3® PROCESS & PRODUCT DESIGN — J.POD® MANUFACTURING DESIGN

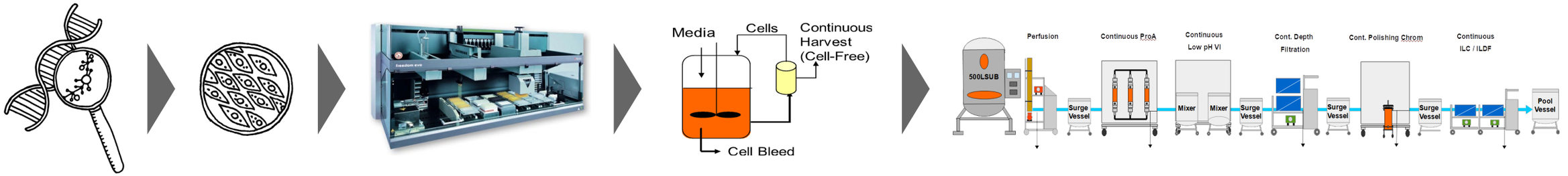
- Powerful expression vectors
- Optimised cell hosts
- Custom media tuned for productivity

- High density perfused culture conditions
- Connected downstream processing
- High resolution analytical methods

- Highly stable formulation conditions
- Current process yields are generally 2-4 grams per reactor/L per day

- Accommodates an array of molecule and process formats, continuous, intensified fed batch, and fed batch

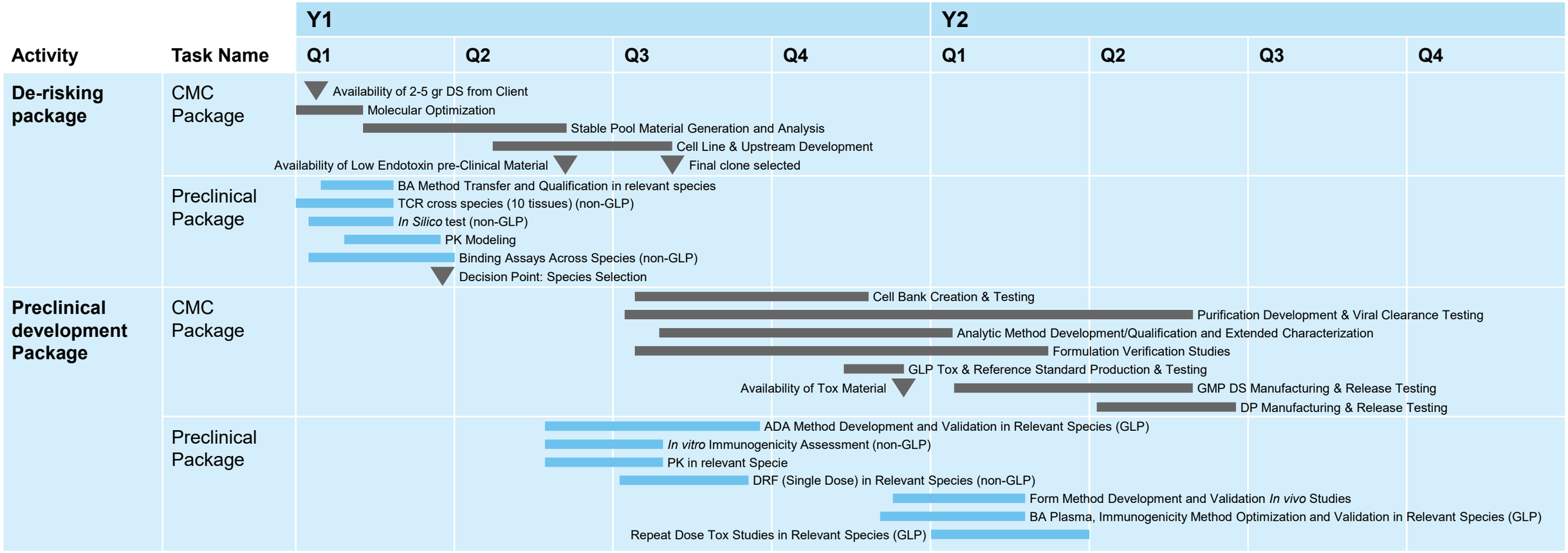
DNA → **Cells** → **Robotics** → **Scale-down system** → **Full scale manufacturing**



A robust platform builds in reliability

Integrated mAb Development

Project Plan (example)

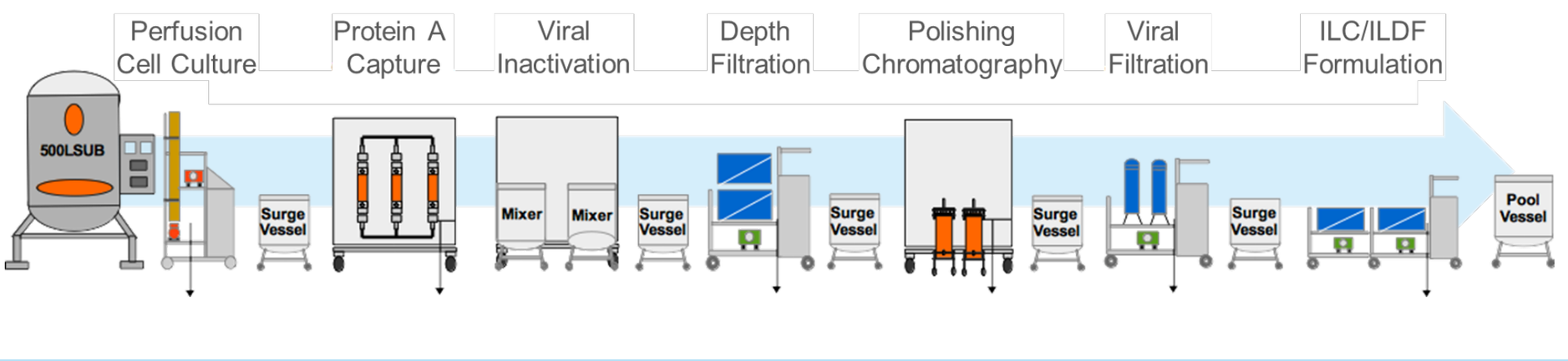


Production processes are small and fit into modular clean rooms that can be reconfigured for flexibility

J.POD® facility design reduces scale-up risk by scaling out, not up

J.DISCOVERY™ — MOLECULE DISCOVERY
J.MD™ — MOLECULE DESIGN
JP3® — PROCESS & PRODUCT DESIGN
J.POD® — MANUFACTURING DESIGN

Intensified continuous processing



Production from a few kilograms to metric tons in the same facility

First J.POD® facility in N. America

Late stage clinical and commercial facility with expanded PD capacity for biologics

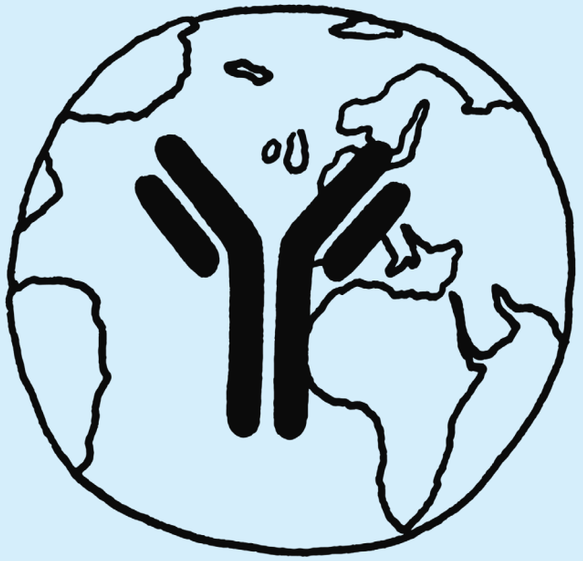
- 130,000 SF facility
- Redmond, WA (near Seattle)
- Deeply experienced and fully capable PD team
- Flexible and accessible PD and manufacturing capacity
- The most advanced manufacturing technologies in a simple facility design

Fully Operational!

The time is now for more access to biologics

Rationale for J.POD® 2 in Toulouse, France[1)]

- Global demand for flexible biologics capacity and for more affordable access to medicines is accelerating
- J.POD®[1)] US in Redmond is on track, demand is strong
- Business Strategy includes large proportion of capacity for co-owned pipeline
- Europe is second largest biologics market with strong desire and rational for security of supply
- Toulouse footprint creates operational efficiency and design for multi-modality biological treatments such as cell therapy adds further synergy with EVT strategic needs – Up to € 50 m from the French government, the Occitanie region, Bpifrance, the Haute-Garonne prefecture as well as Toulouse Métropole



[1)] Subject to local planning, environmental and building regulations and other support and approvals

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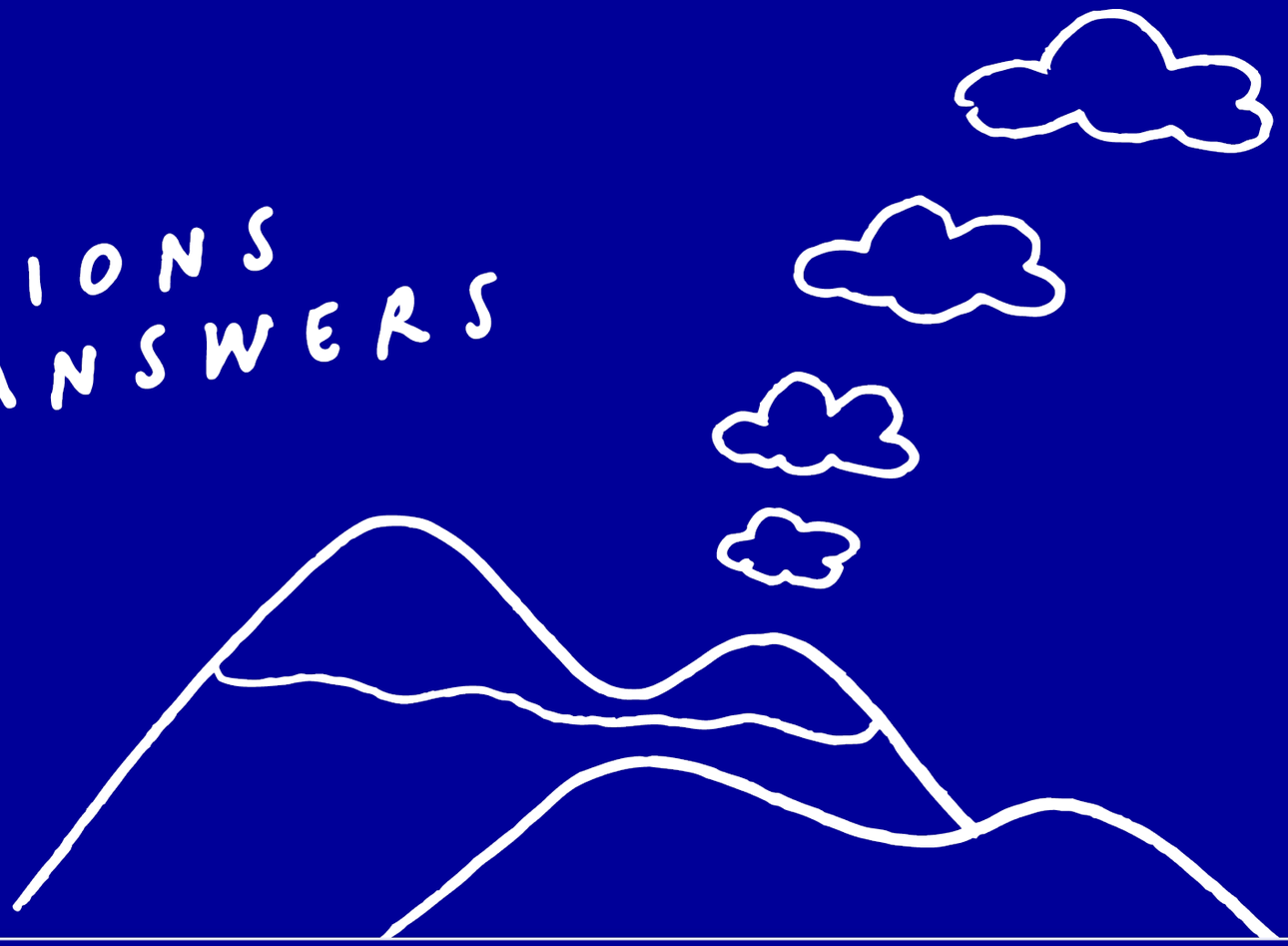
QUESTIONS AND ANSWERS



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