Pre-clinical Development of Antibodies

Which data packages are needed?

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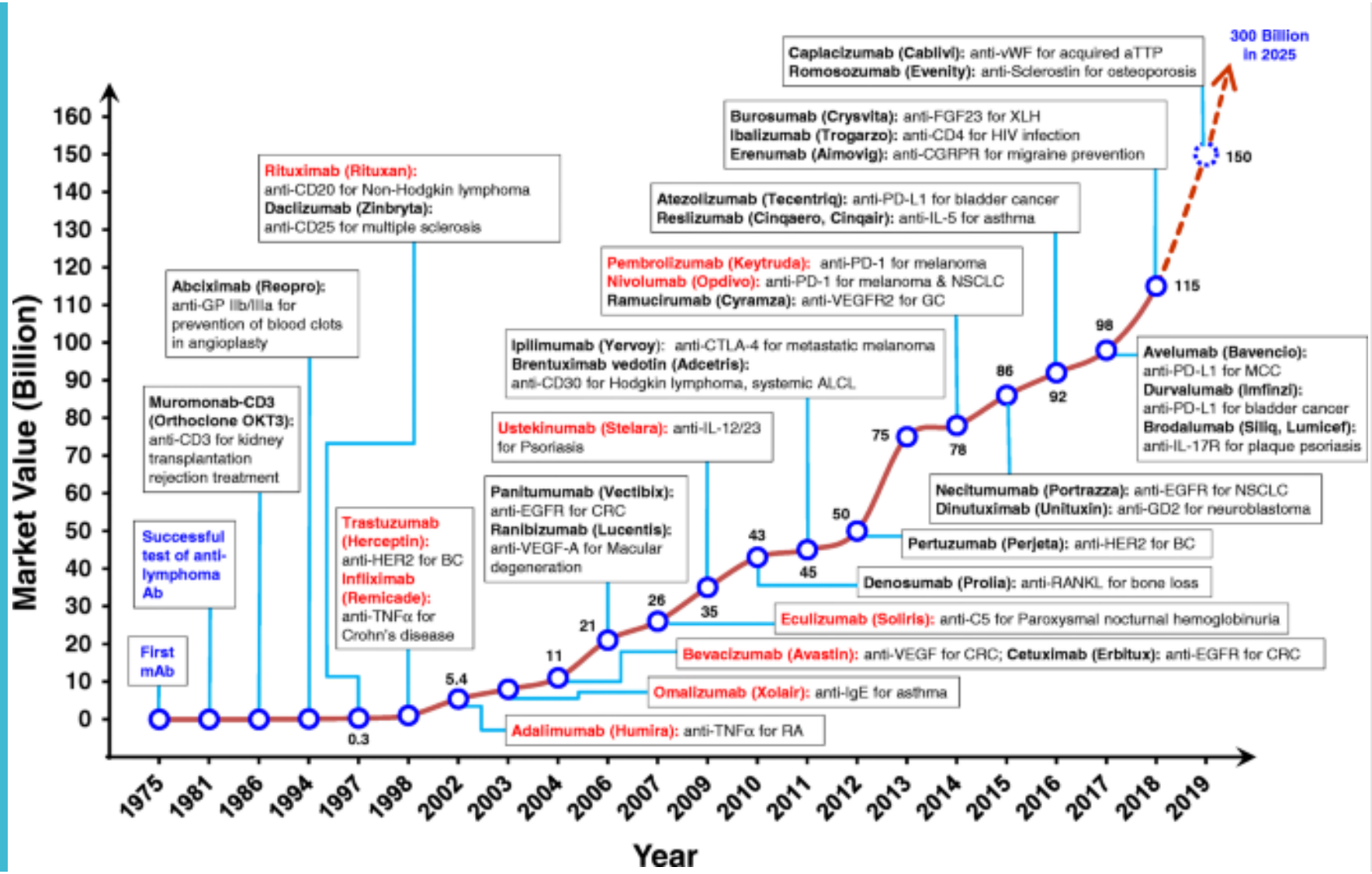
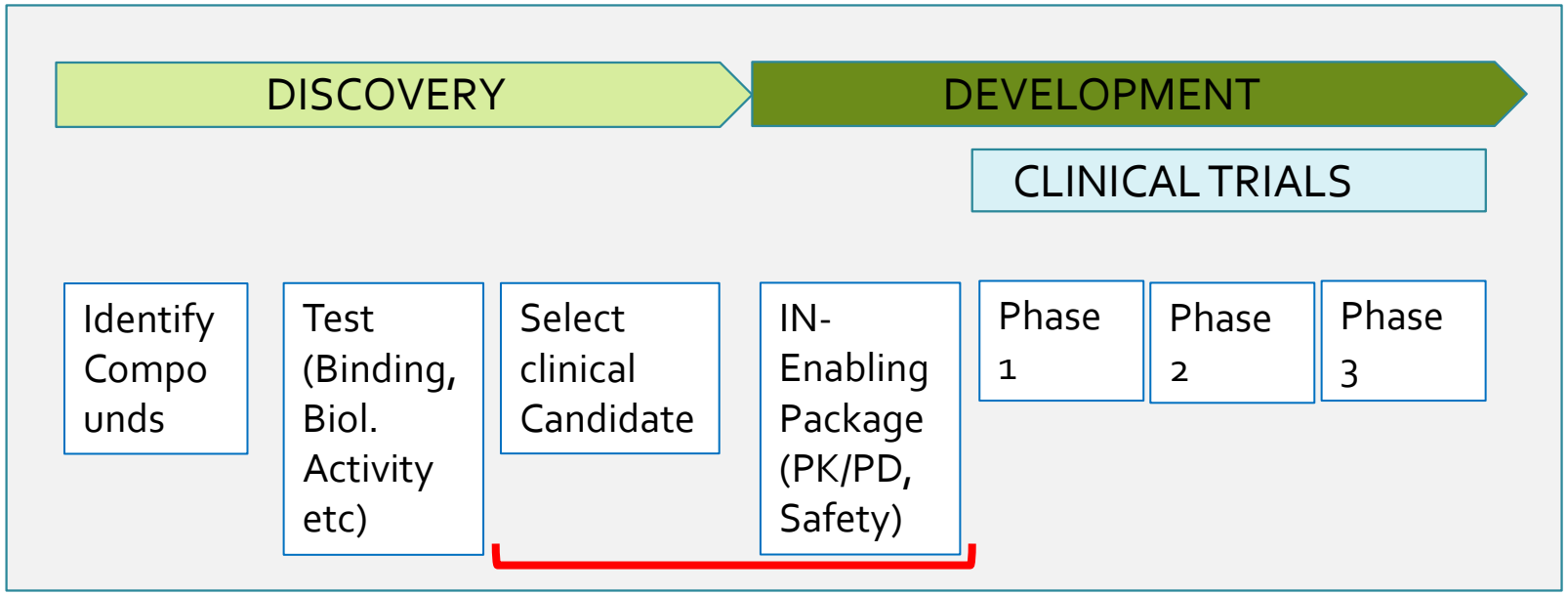
History of Antibody Technology



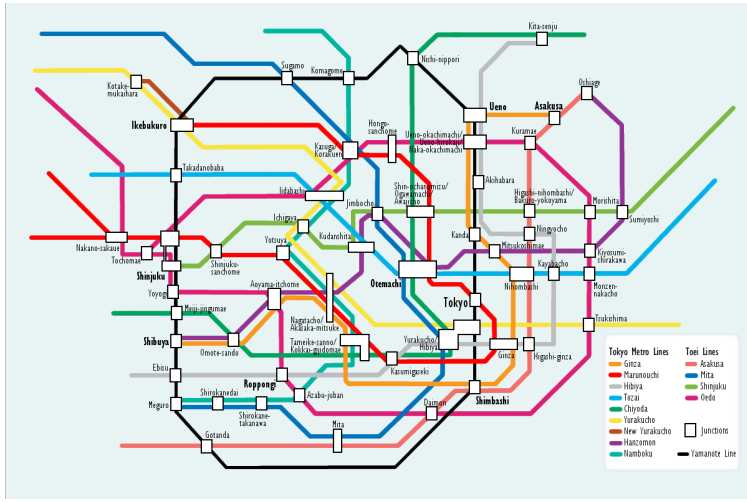
Note: Here only therapeutic antibodies.

Source: L. Yin, www.genscript.com/gsfiles/techfiles/Ab_drug_development_webinar.pdf

The Drug Development Process



Note: Reality is more complex and sometimes feels more like …



Hit to Lead

Congratulations! You have some hits from your antibody screening process.

What next? Transfer your Hits into Leads.

1. Hit selection performed using display technologies, animal immunizations etc.
2. Select Lead Candidates with the desired function (see your TPP) and favourable biochemical, biophysical properties: binding to target; specificity; expressability; in vitro efficacy etc.
3. Epitope mapping
4. Small animal test (usually mouse model): demonstrate in vivo efficacy (POC, proof-of concept)

Lead to (clinical) Candidate

Always have your TPP in mind (which should be optimized along the way).

1. Lead Optimization, as needed:
- Humanization
- Affinity maturation
- De-immunization
- Fc engineering

2. Candidate Characterization:
- CMC-related properties: expression rates, glycosylation, aggregation etc.
- Manufacturability assessment (scalability; final expression system etc.)
- In vivo POC (efficacy) using at least one animal model
- Biodistribution in animals
- Assessment of relevant animal species
- Exploratory PK/PD in animals
- Exploratory safety study in animals

3. Biomarker Development:
- Generate first data set to demonstrate validity of biomarker concept

Prepare for Clinical Development:

(1) „IND-Enabling Package“

The IND Enabling Package is generated according to regulatory requirements. Least headache for you when sourcing it out to a service provider.

1. Pharmacology
   - Safety Pharmacology: Assessment of the effect on the cardio-vascular, neuro-logical and respiratory system of the animals.
   - Primary Pharmacodynamics (PD) to define the theraperapeutic effects of the drug candidate, including dose/exposure relation of effect.

2. Pharmacokinetics (PK)
   - In vitro: metabolism, plasma protein binding.
   - In vivo: repeat dose toxicity to determin Cmax and AUC.
   - ADME: absorption, distribution, metabolism, and excretion (can be postponed and performed in parallel to clinical phase 1)

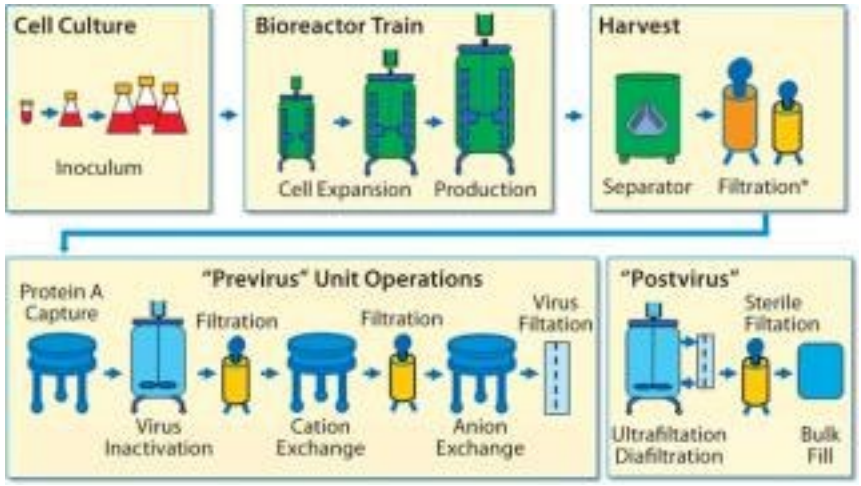
3. Toxicology
   - Acute toxicity (single dose) in two animal species, one of them non-rodent using clinical route of administration plus one parenteral route (e.g. i.v., s.c.).
   - Several doses to determine NOAEL and MTD for clinical dose selection.
   - Maybe in vitro mutagenicity (AMES test), embryo-fetal toxicity, immuno-toxicity (to be discussed with the regulatory authorities).

Prepare for Clinical Development:

(2) CMC

1. During your discovery and over stretches of the non-clinical work, non-GMP manufacturing of the antibody is sufficient.

2. Latest in parallel to the IND-enabling work-package, proper CMC work needs to be performed:
   - Generation of Master Cell Line;
   - Establishment of final Manufacturing Protocol;
   - Establishment of upscaling procedure;
   - Generation of GMP badges for animal experiments (IND pack);
   - Generation of first clinical-grade badge to support FIH study.



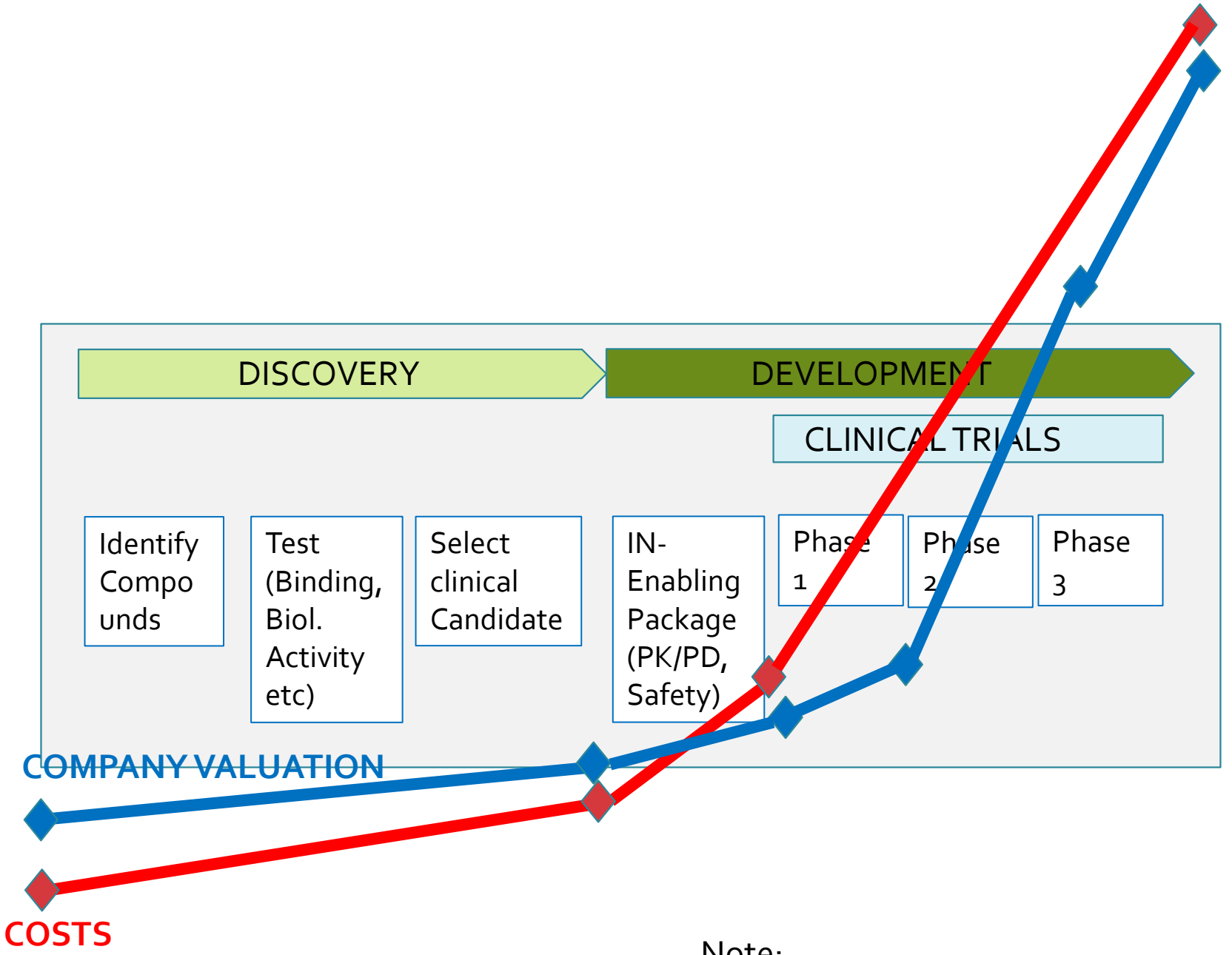
Example of a manufacturing process. Source: B. Minow et al., Bioprocess Intl., Jun 2012

Prepare for Clinical Development:

(2) Documents, Data etc.

1. Evaluation of scientific, technical data packages vs. TPP.
2. Final candidate Safety assessment.
3. Candidate Commercial re-ssessment (based on latest market data).
4. Final legal (i.e. IP) evaluation.
5. Clinical strategy (including CRO selection, logistics etc.), CDP.
6. Clinical biomarker plan.
7. Regulatory planning (including pre-IND meetings with authorities, label etc.).
8. Manufacturing plans, including process, external partners for manufacturing and logistics, fill&finish, packaging.

Planning your costs and value increases



Note:
Here no scale costs/company valuation.

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