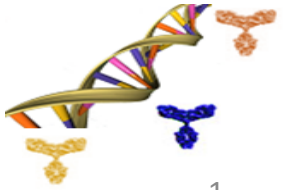
Christine A. Power

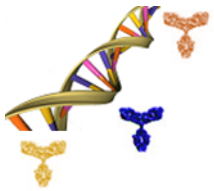
Scientific Evaluation and Due Diligence of Antibody In-licensing Opportunities

4th November, 2021



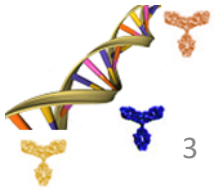
Disclaimer statement

The views, information, or opinions expressed in this presentation are solely those of Dr. Christine A. Power and they do not necessarily represent those of her former employers.



Overview

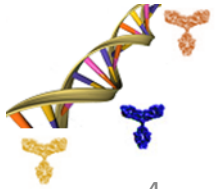
- Importance of in-licensing to the Pharma and biotech industries
- Identification of in-licensing opportunities
- Due diligence process
- Examples (case histories)
- Q&A



Search, Evaluation and Due Diligence Experience

Over 70 evaluations and due diligences (of technologies and molecules) performed between 2006-2020 including:

- DYAX: in-licensing of Fab phage display technology, tech transfer and management of funded antibody discovery projects (Serono)
- Mab factory GmbH: in-licensing of scFv phage display platform, and tech transfer to CRO (for reagent generation) (Merck Serono)
- MSM Protein Technologies: in-licensing of PMPL technology, joint steering committee and project leader (Merck Serono)
- In-licensing of Azymetric bispecific antibody technology from Zymeworks (GSK)
- Evaluation of Macromoltek's *in silico* antibody design technology (GSK)
- Evaluation of intracellular antibody targeting technologies (GSK)
- Evaluation of potential Ab-based therapies against SARS-CoV-2 (GSK)



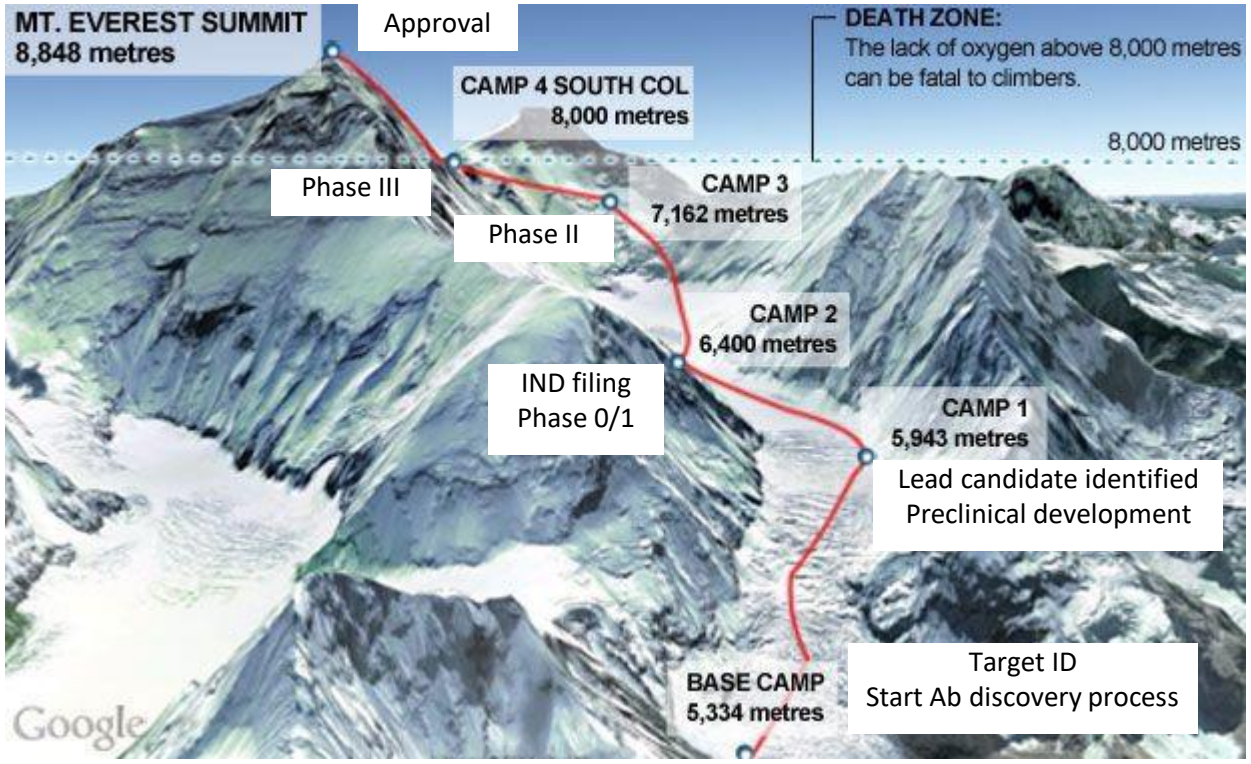
Introduction

Approximately 80% of the FDA approved medicines over the last 10 years were *not* registered by the originator or patent assignee.

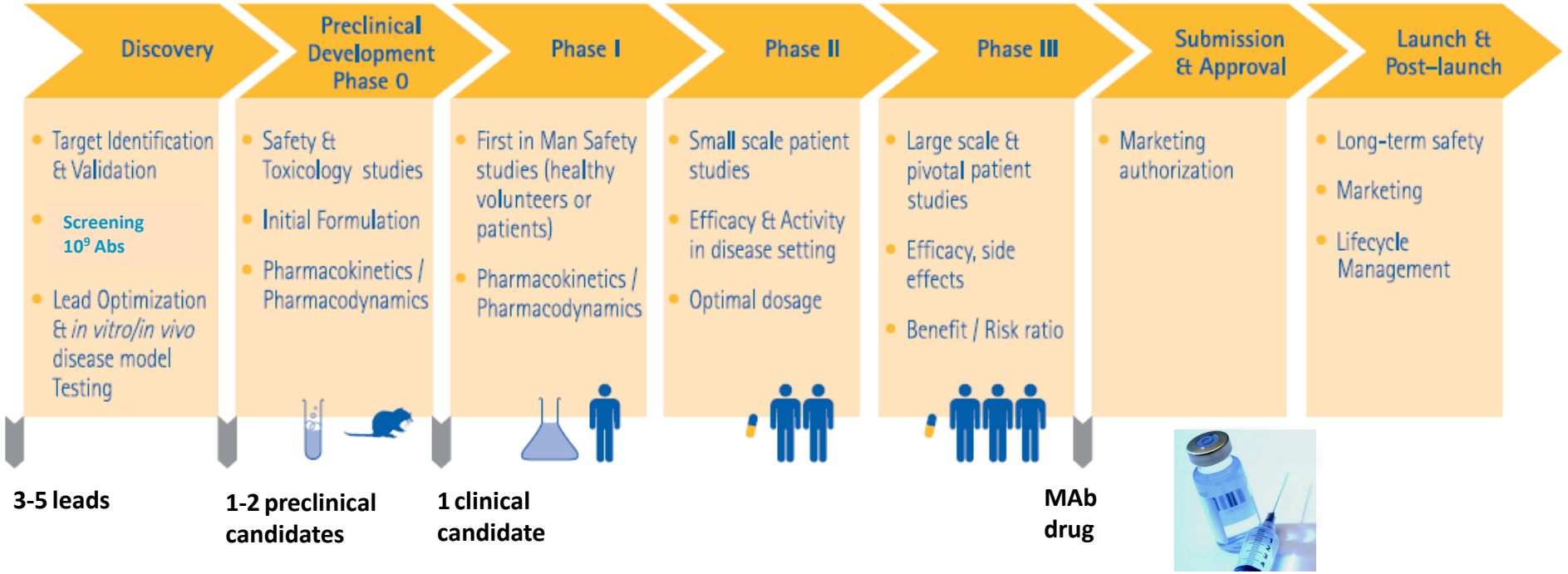
- Many novel therapeutic molecules and technologies are initially conceived and developed by small biotechnology (start-up) companies or universities, but it is usually big pharma/biotech companies that will bring the resulting therapeutics to the market and commercialize the product
- New technologies are also being developed so rapidly that it is more feasible for pharma companies to rely on start-ups for initial drug development in order to acquire de-risked programs at a later stage in development

- Recently there has been a trend for large pharma companies to reduce in-house R&D activities and increase in-licensing or acquisition of products to fill their pipelines - particularly in view of expiring patents

The Challenging Path Toward a Marketed Antibody



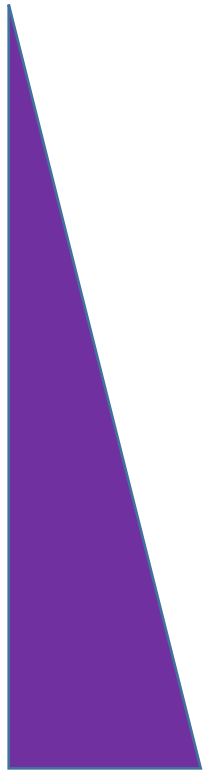
The Challenging Path Toward a Marketed Antibody



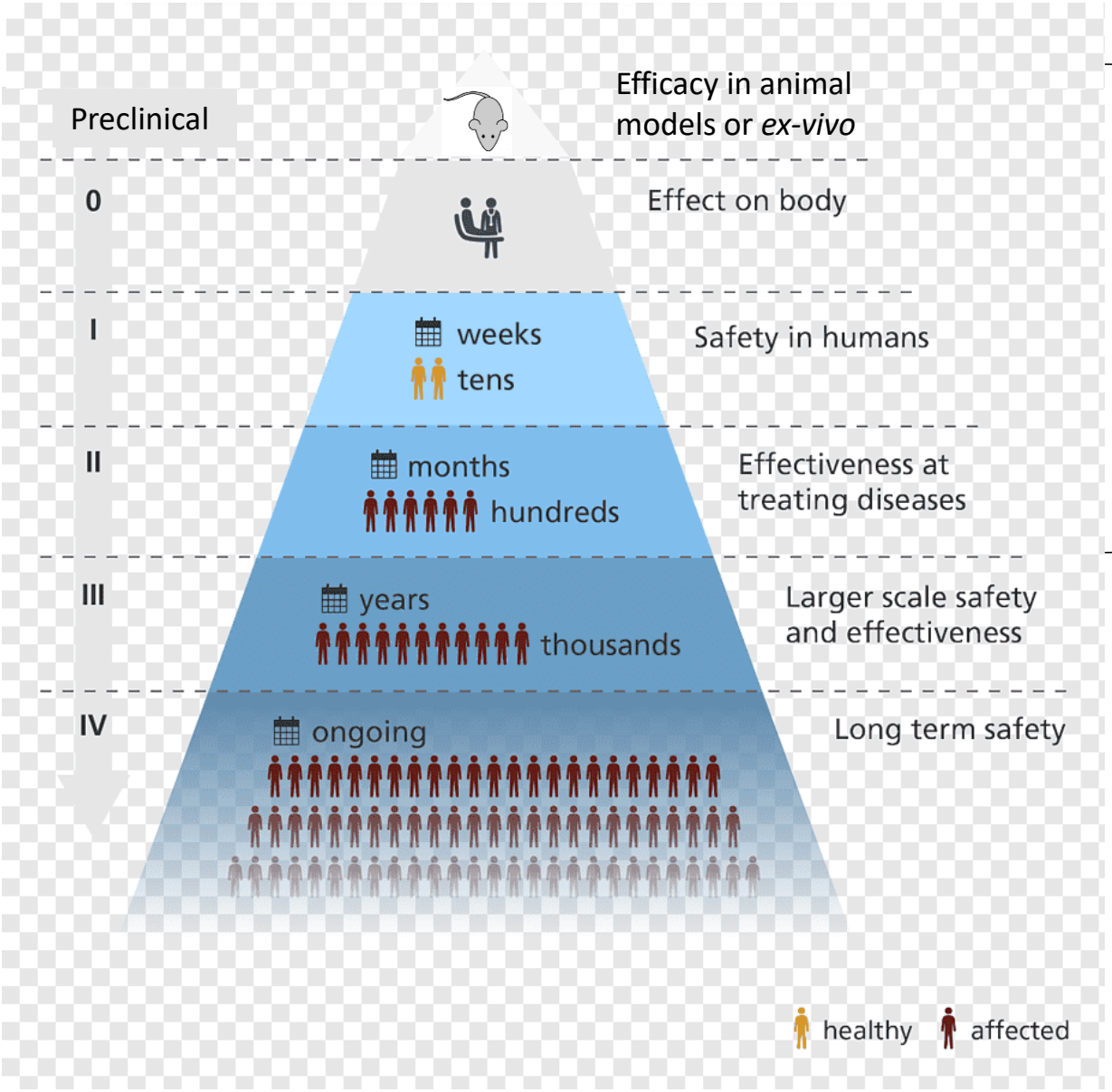
- Average time from discovery to market is >10 years
- Average cost of drug discovery is calculated to be between $1.3 to $2.6 billion
- Average cost of phase III trial is $21.4 million, phase II trial costs $8.6 million, and phase I trial costs $3.4 million*

*Mullard, A. *Nat Rev Drug Discov* **17,** 777 (2018). https://doi.org/10.1038/nrd.2018.198

When are licensing deals made ?



Cost of deal

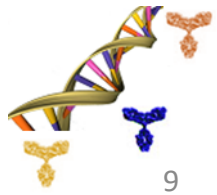


Majority of in-licensing deals

'Haste Makes Waste' In Biopharma Licensing Deals - Manuel Hermosilla, PhD, Assistant Professor, Johns Hopkins University

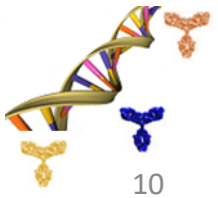
The University or Start-up Perspective

- Forming alliances with partners with manufacturing capability.
  - The licensor may have the resources to fully develop a drug but needs to partner with another company that has the capability to manufacture the product for the market
- Progression of the development of the technology to take the product to market
  - The licensor might be restricted in resources and must partner to take its product through later development phases and into the market
- Exploitation in a different field of application
  - The licensor may have the expertise of exploiting a certain development field, e.g. single indications or diagnostic applications, but might not have the capability or interest to exploit another therapeutic area
- No commercial capability
  - The licensor may be a research institute or a university which does not have the capability to exploit the project commercially at all, and needs to partner with an organisation that does have that capability



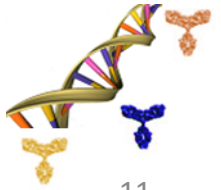
What is due diligence?

- Due diligence is the thorough review and assessment of a potential asset to determine the asset's viability
- Due diligence involves a detailed analysis of available data, relevant regulations, reports, literature and competition to guide informed licensing decisions and negotiations
- A robust due diligence process requires diverse scientific and regulatory expertise to ensure an accurate and holistic evaluation of a potential asset
- A positive outcome should be a mutually beneficial partnership founded on trust and transparency

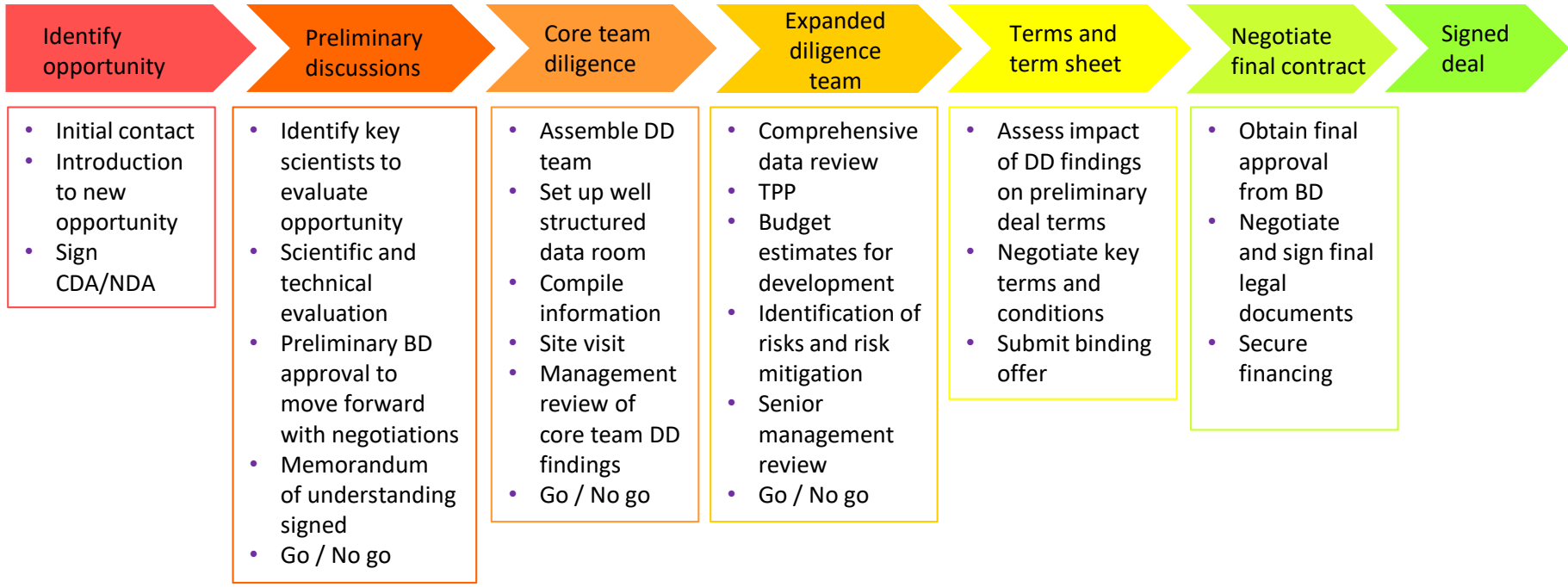


How are opportunities identified?

- Targeted and regular attendance at partnering and scientific conferences
- Scanning of new and recent literature and patent databases to identify emerging opportunities
- Searches of grants, deals, and pipeline databases
- Outreach and networking with university tech transfer offices, KOLs, industry contacts, and licensing professionals
- Direct approach from start-ups or university researchers or TTOs to present their asset(s)



Search, Evaluation and Due Diligence Process

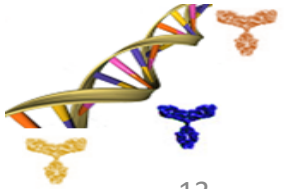


- Time taken for the due diligence process can vary from months to 1-2 years depending on the developmental phase of the asset

Adapted from Parasrampuria D. et. al 2020
Drug Discovery Today 25 (10) 1855-1864

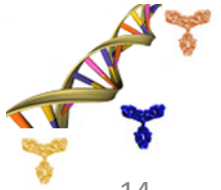
Search and Evaluation – What We are Generally Looking For

- Potential strategic fit of each unique opportunity
- The molecule addresses novel disease biology and targets a protein with first-in-class potential
- The molecule is a lead candidate, preferably in lead optimization stage
- The molecule has demonstrated efficacy in disease-relevant cellular and, depending on the stage, in *in vivo* models
- Best case scenario - the molecule is IND-filing ready



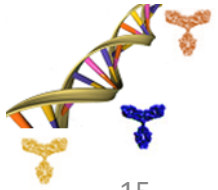
Evaluation of New Technologies

- Is the technology cutting edge?
  - Will it open up target space (e.g. access to targets currently undruggable with antibodies)?
- Is it proprietary?
  - IP and possible infringements of others' patents
  - Are there any related or competitive technologies?
- Is there a sound scientific basis?
- Is it transferable?
- Will this technology work?
  - Do you have PoC studies?
- What are the strengths and weaknesses?
- Is the research idea novel and the technology interesting enough to be funded?
- Is it a platform technology with multiple future applications?



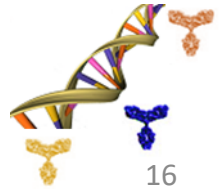
Due diligence – who is involved?

- Depending on the developmental phase of the asset, the Business Development (BD) team identifies expert consultants in:
  - Research
  - Preclinical development
  - Clinical development
  - CMC and supply chain
  - Regulatory
  - Market and payer research
  - Intellectual property



What are the key questions that need to be answered during DD? (1)

- Does the asset address an unmet medical need?
  - Are there supporting scientific data and are those data sufficiently compelling?
  - Is there sufficient differentiation from competitors
- Is the product candidate proprietary? Is there Intellectual Property (IP) protection in place?
  - Exclusivity and freedom to operate, both hinge on the intellectual property rights
  - Patents and know-how each provide market exclusivity, precluding competitors from taking market share for a certain period of time
- Can the asset be manufactured?



What are the key questions that need to be answered during DD? (2)

- Is the project/business truly in the condition that is being presented? Have any corners been cut, are there any gaps?
- What are the risks and are risk mitigation strategies in place?
- What is the pathway to market and to value realization ?
  - How long will it take?
  - How much will it cost?
- Is there scope for a ‘killer experiment’ to yield a definitive go/no-go decision?
- Does the organisation have the right team for the job?

Key Data Required for DD Depends on Asset Stage

Preclinical (discovery through to IND filing)

- Formulation and solubility compatible with proposed route of administration
- Concentration required for adequate receptor occupancy/target engagement
- Potency in relevant cellular assays
- POC in animal models
- PK in rodent/cyno compatible with proposed dosing regimen in humans
- PK/PD model is predictive when scaled to human
- No ADAs or unlikely to be a liability
- Any safety or tox signals?
- Suitable yield of drug substance from predictive small scale cultures
- Commercialisable cell line
- No insurmountable physical or chemical stability issues during processing and storage
- No unmanageable sequence heterogeneity

Early clinical development (FIH to Ph. IIa)

- Safety as assessed by clinical laboratory values, adverse events, ECG
- PK, dose proportionality/ linearity of exposure
- Pharmacodynamic (PD) changes – changes in biomarkers with time – PK/PD relationships
- Exploratory Exposure- Response analysis for safety and efficacy endpoints
- Validated analytical methods for measuring drug concentration, ADAs, and any biomarkers to be used for regulatory decision making ; diagnostic methods being developed
- Clinical trial design should reflect the demographic distribution of the target patient population.

Late clinical development (Phase IIb/III)

- Overall clinical efficacy, and efficacy in subpopulations should be similar
- Confirm that does and dosing regimens are appropriate for overall populations and subpopulations
- Bridging studies for any changes in formulation (or change in manufacturer)
- Benefit/risk evaluated for overall population and subpopulations
- Study design and clinical endpoints agreed upon with regulatory agencies
- Diagnostic tests, if available are approved and will be commercially available

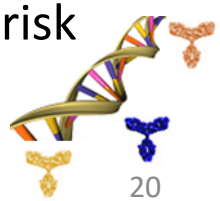
Adapted from Parasrampuria D. et. al 2020 Drug Discovery Today 25 (10) 1855-1864

Important considerations - Preclinical, Ph 0/I assessment

- For early-stage preclinical asset, the questions will be related to formulation, developability, receptor occupancy/target engagement, acute and long-term toxicity, preclinical assessment of metabolic pathways, tissue distribution, translatability, and projected dose
- Where animal models can provide meaningful data, the design of the FIH clinical trial can be optimized
- In cases where preclinical data are limited e.g. animal model data due to lack of cross-reactivity or transgenic mouse models not available, often the FIH studies would be used to generate safety data through the clinical trial itself
- A Phase 0 trial might be performed in a limited number of subjects at a low dose to gain understanding of the mechanism of action (MOA), bio-distribution, tumour targeting, PK, or to guide selection of dosing route

Clinical development

- Has the relationship between the target/phenotypic assay and disease been established?
- How does target expression vary across tissues?
- Have the target-related and off-target safety margins been established?
- Can an exposure/response relationship be generated *in vivo* to demonstrate proof-of-concept?
- Can biomarkers of each stage of the exposure/response relationship be generated to measure this both in preclinical and early clinical testing?
- Is the indication chosen appropriate and does it offer the fastest path to prove efficacy?
- Does the trial design answer the key questions and give a basis to continue development if successful?
- Does the therapeutic hypothesis work with meaningful clinical benefit?
- Are any safety concerns sufficiently understood and able to be managed to an appropriate risk level?



Clinical trials

- Clinical trials should reflect the demographic distribution of the target patient population. Women are generally under-represented

- For due diligence, it is imperative to assess whether clinical trial data are representative of the patient populations from the perspective of demographics, genetics, and molecular determinants of therapy to ensure that the right patient and right dose for that patient population has been identified

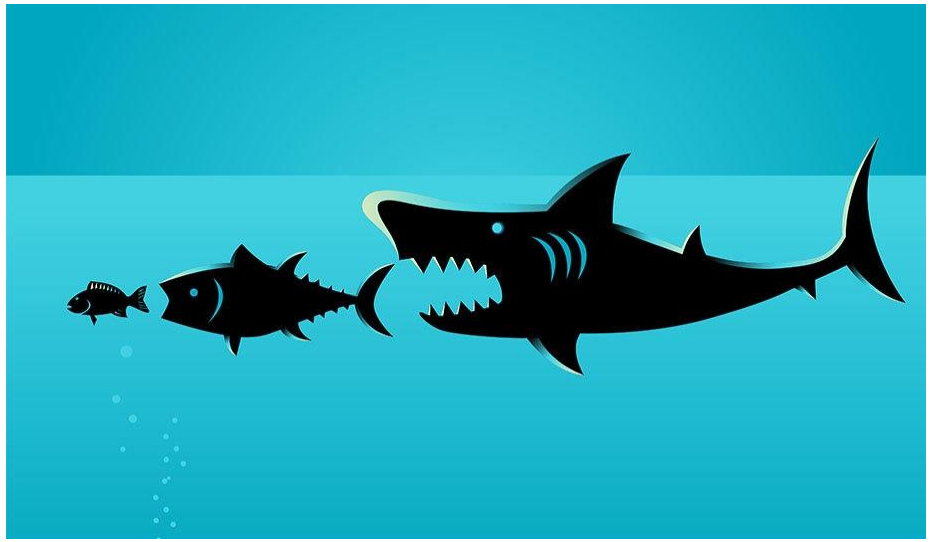
- It is also important to ensure that appropriate diagnostics are being developed for enabling precision medicine, for identifying patients most likely to benefit from a novel therapy, and for stratifying patients to the appropriate dose/dosing regimen in clinical trials

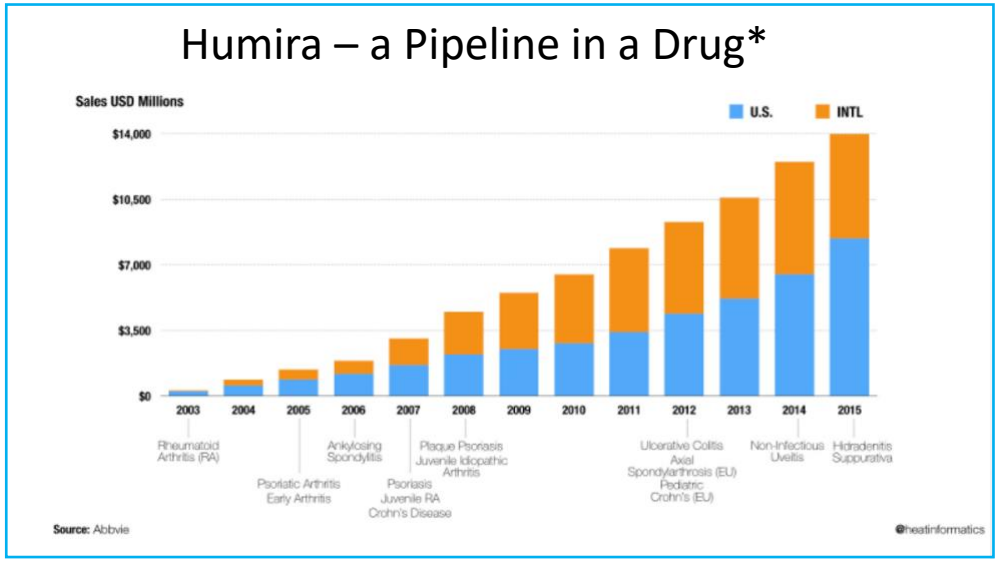
Due diligence findings can also be negative….

- Commercial and market access issues
- No differentiation from competitors
- Potential CMC issues
- Negative risk-benefit
- Insufficient data for IND filing
- Disconnect between development plans and commercial timelines
- Negative KOL opinion regarding use in specific geographic locations

The Story of Humira® – the Antibody that Keeps Giving

- Cambridge Antibody Technology (CAT) Group plc a spin off from MRC developed phage antibody library technology for discovery of human antibodies (1991)
- BASF signed a collaborative research agreement with CAT to access its patented phage display technology (1994)
- BASF released positive results for the anti-TNF antibody D2E7 in a Ph. I RA trial involving 140 patients (1998) and then a Ph. II study on 283 patients (1999)
- BASF initiated Ph. III trials in 2000
- Abbot acquired BASF pharma in 2001
- Abbot submitted BLA to US FDA for D2E7 (now called Adalimumab) and EMEA for approval to market the mAb for RA (2002)

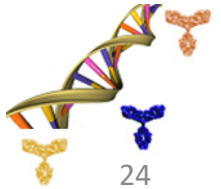




*https://www.linkedin.com/pulse/story-humira-swiss-army-knife-pharmaceutical-drugs-tuhin-a-rahman/

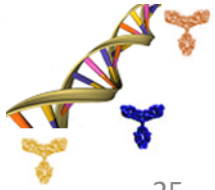
The Value of Asset Scouting

- GSK recently acquired Tesaro for approximately $5.1 B USD
- Tesaro's pipeline was sourced through business development partnerships, collaborations, and in-licensing of oncology assets
- Tesaro was able to identify unique oncology assets and subsequently acquire or partner on the development and commercialization of those assets
- Their drug pipeline, comprised of an FDA-approved PARP inhibitor (Zejula®) currently under evaluation in one phase III and five phase II studies, three additional novel drugs in phase I studies, and several more in discovery



Case history 1
Unforeseen problems after in-licensing

- Antibody phage display is the most widely used *in vitro* selection technologies for antibody discovery
- Access to antibody phage display was controlled by a few companies, based on their technology patents
- The DYAX Fab-phage display antibody technology was in licensed by Serono in 2006, after evaluation of a number of Ab companies including CAT, XOMA and Morphosys
- As well as using the technology in house, Serono initiated a number of funded research programs one of which ended successfully with the discovery of Avelumab aka Bavencio (an anti PD-L1 mAb first approved in 2017)



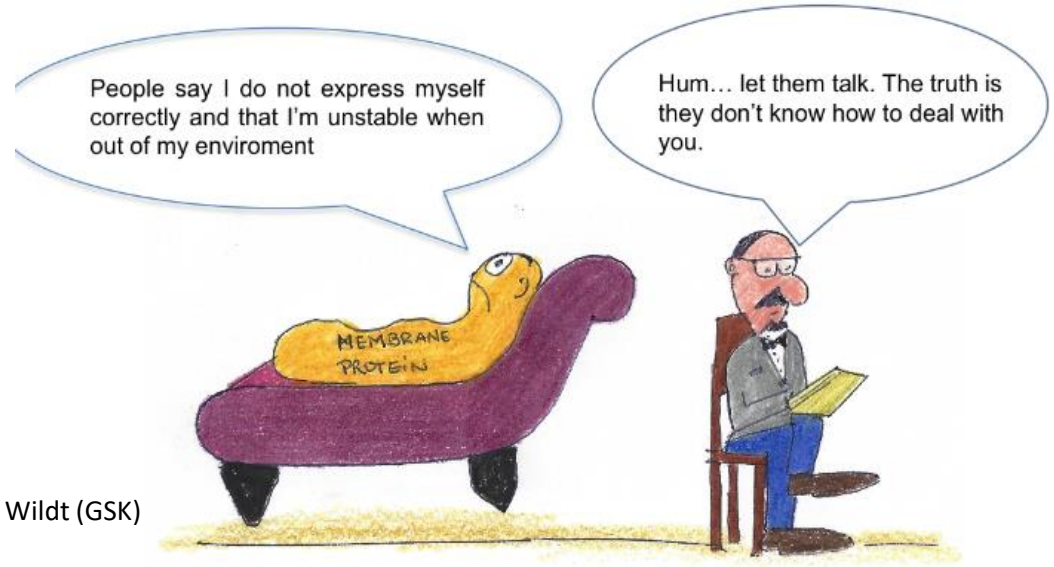
Case history 1 (contd)
Unanticipated problems after in-licensing

GATEKEEPING

- Development of antibodies using the Dyax antibody technology were subject to gatekeeping
- The gatekeeping process instigated by phage display companies is a process that determines if you are able to pursue development of antibodies against a nominated target
- A number of MerckSerono's nominated targets failed the gatekeeping process
- Mitigation strategy was to in-license a new scFv phage display library in 2009, which was free from target gatekeeping restrictions

Case history 2
Generating functional antibodies against GPCRs

- More than 800 members of the GPCR protein family have been identified so far, and sales of drugs targeting GPCRs account for 27% of the global drugs market
- Pharmaceutically, GPCRs are extremely important targets but they are notoriously difficult to work with



Courtesy of Ruud M De Wildt (GSK)

Progress with multi-spanning membrane protein mAb discovery

1998 – Buell et al
Whole cell immunization used to isolate functional Abs (P2X7)

2000 – Mirzabekov et al
First use of paramagnetic proteoliposomes to isolate functional Abs by phage display (CCR5)

2003 – Chowdhury
First demonstration of DNA based immunization to isolate functional Abs

2005 – Zhang et al
First use of cyclic peptide to isolate functional Abs with phage display (CCR5)

2011 – Willis et al, Hotzel et al
First use of virus-like particles as immunogen and for phage selection

2012 – Mogamulizumab
First chemokine receptor mAb approved in Japan

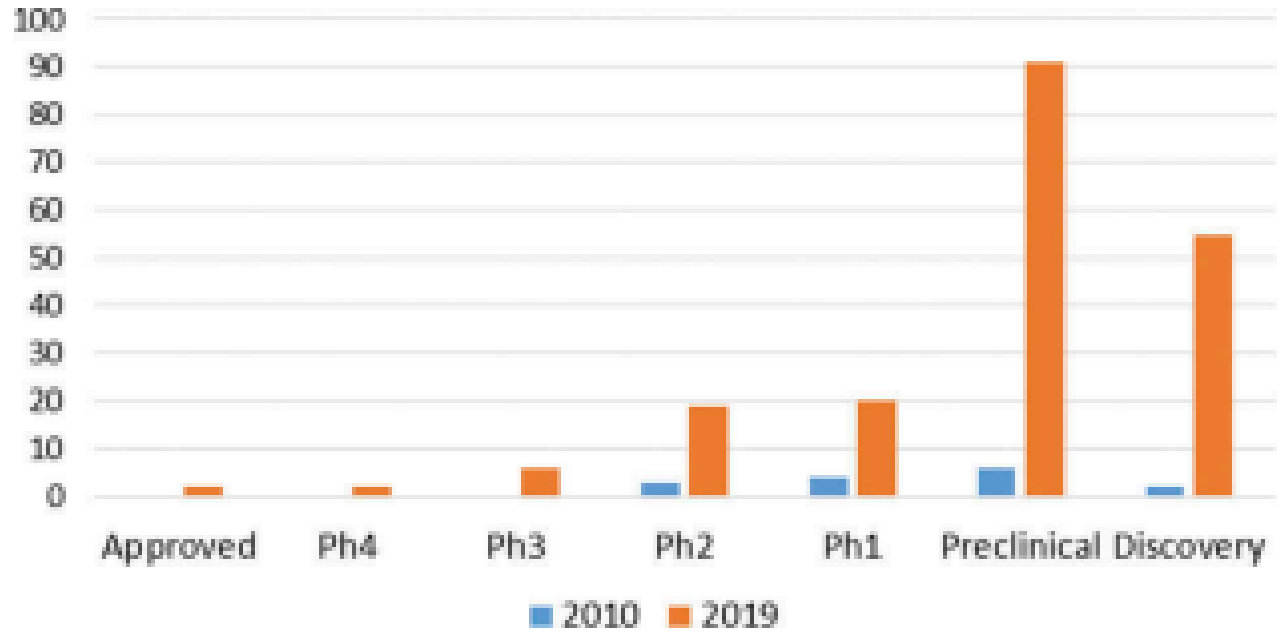
2014 – Hutchings et al
First use of stabilised GPCR receptor to isolate functional Abs (β1AR)

2015 – Ahuja et al
First use of chimeric proteins to stabilise Ion channels with small ECL ($Na_v1.7$)

2018 – present day
2 approved anti-GPCR mAbs (mogamulizumab and erenumab) and approx. 170 in clinical trials

Slide adapted from: Ruud M De Wildt (GSK) Progress and challenges with the isolation and optimization of antibodies against Multi-Spanning Transmembrane Targets (2018).

Anti-GPCR antibodies in development*

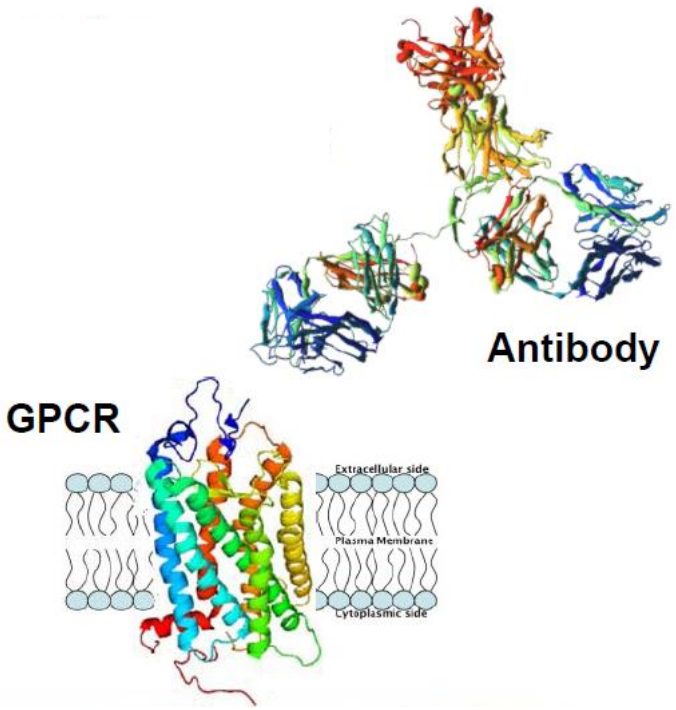


*Catherine J. Hutchings (2020) A review of antibody-based therapeutics targeting G protein-coupled receptors: an update, Expert Opinion on Biological Therapy, 20:8, 925-935, DOI: 10.1080/14712598.2020.1745770

Why is it technically challenging to generate antibodies against GPCRs?

- **Native conformation is necessary to generate functional (neutralizing) Abs**
  - Difficult to express and purify GPCRs to homogeneity whilst maintaining the native state
  - HEPTARES

- **Antibodies generated against peptides rarely recognize the native receptors**
  - PEPSCAN, PROGENOSIS

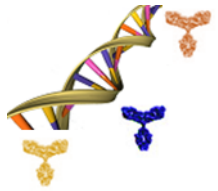


- **Poor antigenicity** - only about 10-20% of the GPCR is exposed on the cell surface (limited epitope space)

- **Low receptor density** of receptors on cell surface in primary cells

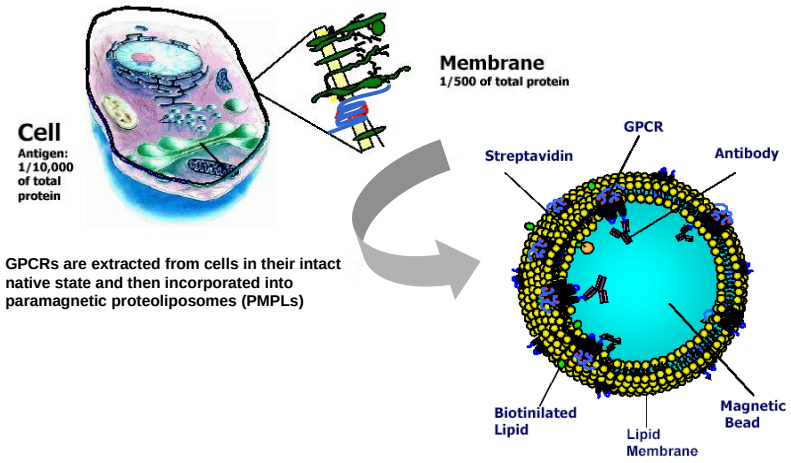
- **High degree of homology** between human and mouse receptors means it is difficult to break tolerance using immunization
  - EPITOMICS

- **Complicated biology** – multiple conformations/ activation states; constitutive activation; redundancy of ligand/ receptor pairings etc.



Case history 2
Generating functional antibodies against GPCRs

- We evaluated a number of different technology platforms (Heptares, Pepscan, Epitomics, Progenosis, Integral and MSM Protein Technologies)
- MSM, a start-up based near Boston was selected for due diligence as they had developed a proprietary paramagnetic proteoliposome (PMPL) technology that seemed most likely to produce functional antibodies



GPCRs in PMPLs are:

- **in the correct orientation**
- **in the native state**
- **pure**
- **highly concentrated**
- **retain ligand binding affinity and selectivity**

Case history 2 (contd)
Generating functional antibodies against GPCRs

At first things did not go according to plan……

1. A key member of staff at MSM who had the necessary screening experience left the company just before the program start
2. The two way tech transfer did not work:
   - MerckSerono were not allowed to transfer the DYAX phage display library to a third party for screening so library screening had to be done at the Merck Serono facility in Billerica
   - MSM wanted to keep their know-how on preparation of the PMPLs secret so PMPLs were prepared at their Waltham, Mass facility

…….but ended well

- Neutralizing CXCR5 antibodies for treatment of MS were successfully generated. US Patent US953405B2 (2017)

Case History - 3

What's wrong with my antibody?

- Promising anti-MMP mAb discovered at Weizmann Institute after using a novel Zn-tripod immunisation strategy*
- Antibody purified from hybridoma was active in mouse model of IBD* and EAE model (unpublished)
- Recombinant antibody was produced in HEK293 cells after VH and VL cloning from the hybridoma cell lines
- The recombinant antibody did not bind to its target even though the sequence was confirmed correct by protein sequencing of the antibody purified from the hybridoma!

*Sela-Passwell N., et al. Antibodies targeting the catalytic zinc complex of activated matrix metalloproteinases show therapeutic potential. Nat Med. 2011 Dec 25;18(1):143-7. doi: 10.1038/nm.2582. PMID: 22198278.

WHAT HAS BEEN SEEN…….
cannot be unseen

Case History - 3

What's wrong with my antibody?

- Promising anti-MMP mAb discovered at Weizmann Institute after using a novel Zn-tripod immunisation strategy.*
- Antibody purified from hybridoma was active in mouse model of IBD* and EAE model (unpublished).
- Recombinant antibody was produced in HEK293 cells after VH and VL cloning from the hybridoma cell lines.
- The recombinant antibody did not bind to its target even though the sequence was confirmed correct by protein sequencing of the antibody purified from the hybridoma!
- Conclusion that simple expression of the correct VH and VL does not necessarily ensure a functional mAb, as contribution from other absent Ig sequences, post translational modifications or secondary or tertiary structure may limit antigen binding properties.
- Collaboration was not pursued.

*Sela-Passwell N., et al. Antibodies targeting the catalytic zinc complex of activated matrix metalloproteinases show therapeutic potential. Nat Med. 2011 Dec 25;18(1):143-7. doi: 10.1038/nm.2582. PMID: 22198278.

SARS-CoV-2

- The outbreak of COVID started a rush to develop antibody-based drugs, primarily led by big pharma and biotechs
- From March – May 2020, GSK received an unprecedented number of collaboration proposals for antibody-based and small molecule drugs, vaccines and technologies that could be developed to treat COVID or be useful for future outbreaks

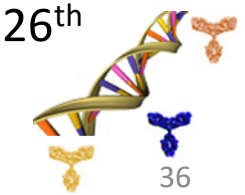
VIR

GSK and Vir Biotechnology enter collaboration to find coronavirus solutions

April 6, 2020

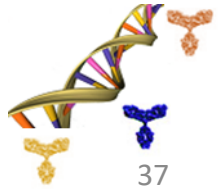
- Companies will combine their unique scientific and technical expertise to combat COVID-19 and potential future coronavirus outbreaks
- Promising antibody candidates for SARS-CoV-2 to be accelerated into phase 2 clinical trials within the next three to five months
- GSK to make equity investment of $250 million in Vir

- Sotrovimab (VIR-7831) a monoclonal antibody used in the treatment of COVID-19 that the two companies developed together, was granted Emergency Use Authorization by the U.S. FDA on 26th May, 2021



Conclusions

- Due diligence is a fundamental and necessary exercise prior to starting any in-licensing of a molecule or technology, or collaborative product development, and should be an ongoing process
- The due diligence process requires sufficient expertise and experience and a manageable process and timeline
- Identify any potential ‘land mines’ and have mitigation plans prepared to side step them
- If due diligence reveals that a product or technology is unlikely to succeed - for any reason - it’s better to cut one’s losses and stop
- For any deal to be truly successful, both sides need to show trust and transparency, and come away from the negotiating table with the sensation of a win



Contact Details

www.linkedin.com/in/christine-a-power

Christine A. Power - Career History

- Ph.D in Biochemistry (University of Surrey *'Effect of genotoxic compounds on the fidelity of DNA synthesis'*
- Postdoctoral research at MRC Toxicology Unit, Carshalton, UK
- Postdoctoral research at Ciba-Geigy AG., Basel, Schweiz
- British Biotechnology, Oxford, GB
- Glaxo Institute for Molecular Biology, Geneva, Suisse
- Serono Pharmaceutical Research Institute, Geneva, Suisse
- Merck Serono S.A. Geneva, Suisse
- Drugs for Neglected Diseases Initiative, Geneva, Suisse
- Novartis Consumer Health, Nyon, Suisse
- Arsanis Biosciences, Vienna, Austria
- GlaxoSmithKline, Stevenage, UK