Small molecule Translation: from target to adopted product

Guidance document for PIs

May 2020

Translational Research Office (TRO)

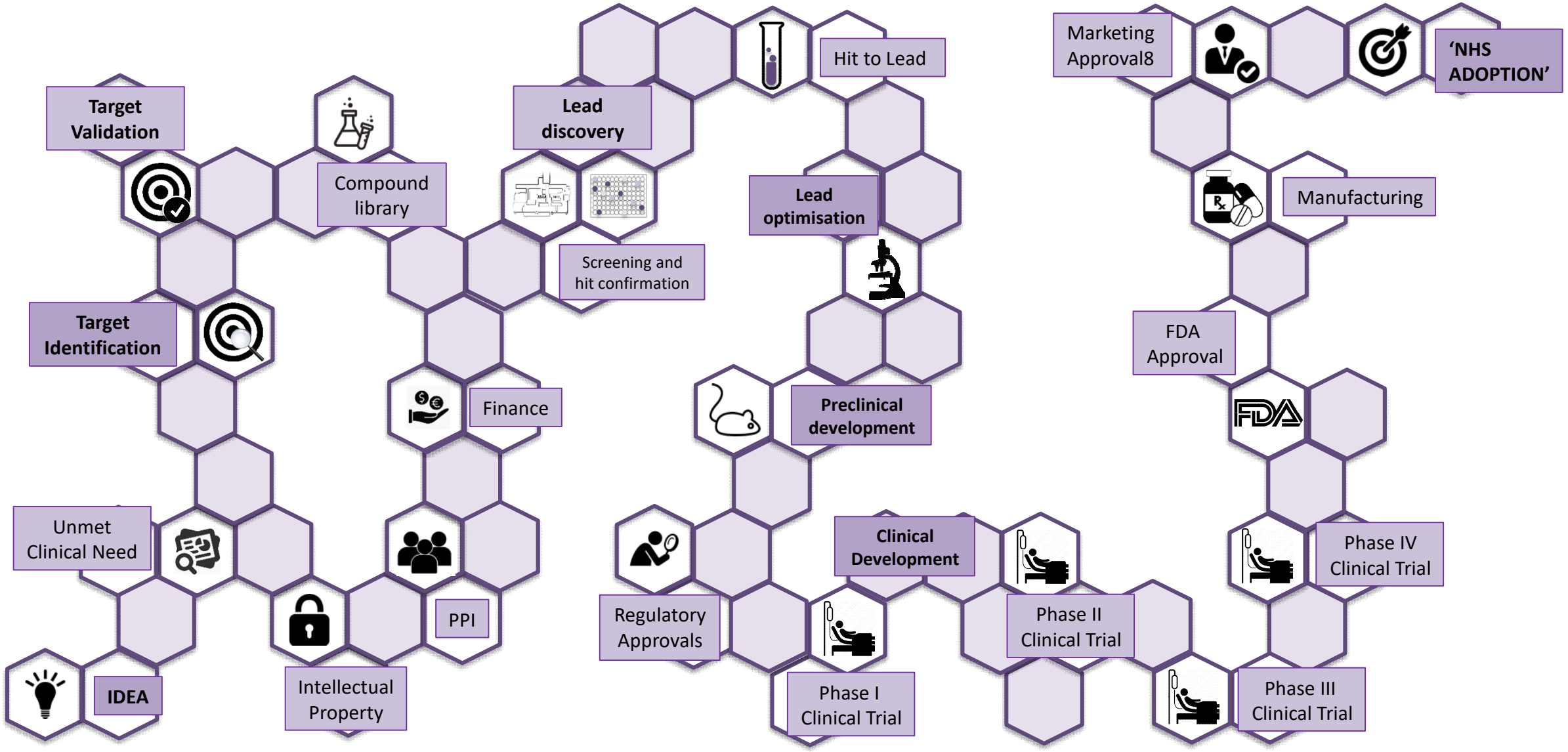
Translational Research Office
www.ucl.ac.uk/translational-research/

Small molecule Innovation Network
www.ucl.ac.uk/slms/ovph/TINs

Objective:

- Provide a workflow summarising key activities and considerations for development, evaluation and commercialisation of small molecule, to facilitate their effective translation into the clinic.

Work Flow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Compound library
Lead discovery
Hit to Lead
Screening and hit confirmation
Lead optimisation
Target Identification
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Preclinical development
Unmet Clinical Need
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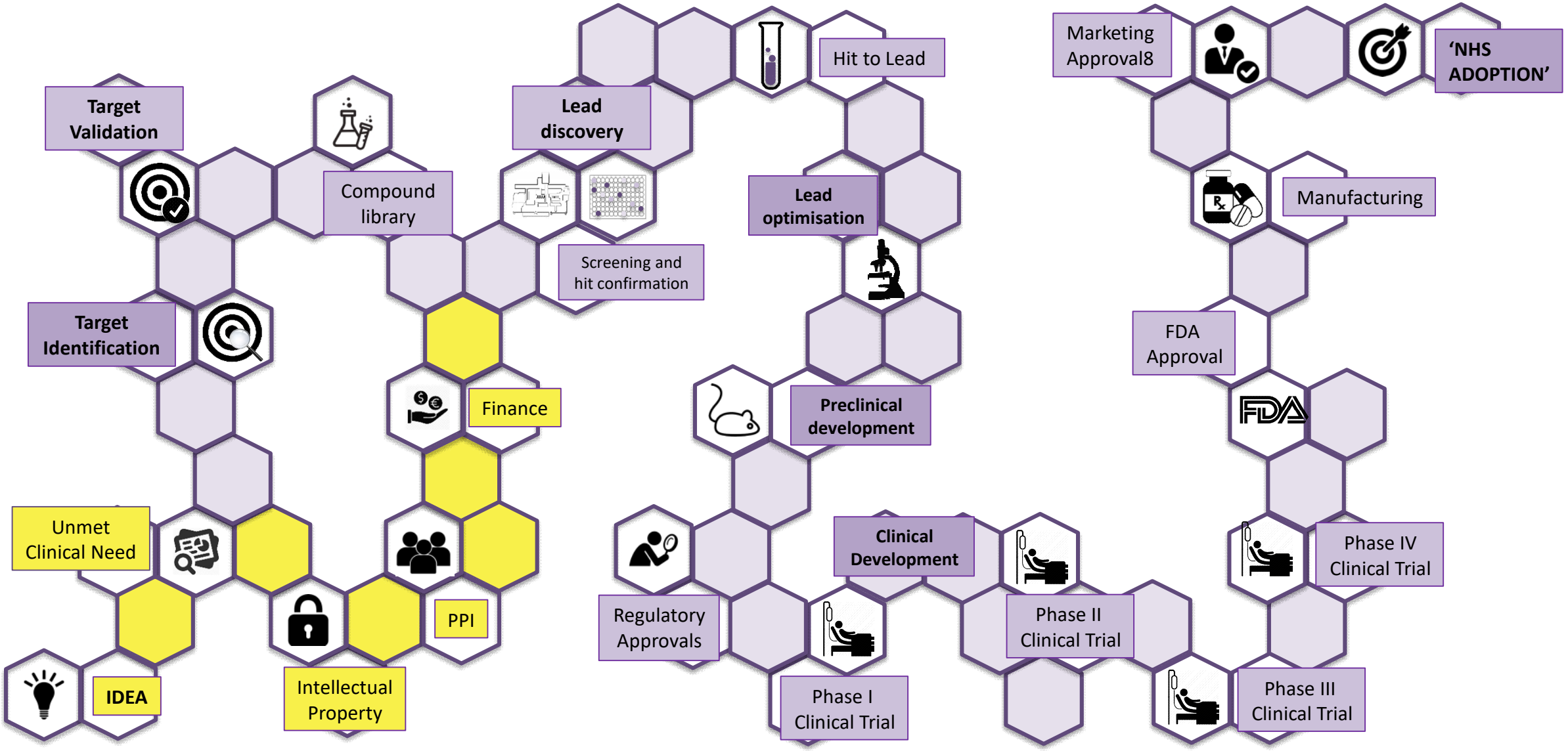
Considerations

1. Project Team
2. Therapeutic design and Planning
3. Target identification and Validation
4. Lead discovery
5. Lead optimisation
6. Preclinical development
7. Clinical Development (phase I-III)
8. Commercial Adoption

Work Flow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1. Project Team








- Successful translation of an idea into a NHS-adopted therapeutic is reliant upon the consideration & effective decision-making of a diverse group of individuals
- The input from experts <u>throughout</u> the product's development path is essential and a project team should be formalised early, including key members & responsibilities:
- Team composition will change during the lifetime of a project but at the discovery phase teams are usually composed of the following-

Chair	Project Management	Medicinal chemist
Enzyme pharmacologist	Target biology expert	Behavioural pharmacology expert
Analytical chemist	Organic chemist	DMPK expert

- The team should meet regularly to ensure continuous review of progress, awareness & relevance to the clinical and competitor landscapes and to ensure <u>decisive project advancement</u>

Therapeutic Design & Development

IDEA:

- **Target Product Profile (TPP)** – captures the 'benefit' of the proposed therapeutic and key considerations in the strategic development of the product (incl. technical, scientific and medical information required to satisfy key stakeholders (regulators and funders))

<u>TPP headings</u>

- Intended use
  - *Indications, target patients, health economics*
- Drug description
  - *Dosage, administration route, dosage forms*
- Risk/Side Effect
  - *Contraindications, adverse reactions, overdosage*
- Non-clinical testing
  - *Toxicology, efficacy, drug stability, regimen, duration*
- Clinical testing
  - *Relevant safety & efficacy end points, storage, handling*

<u>Longer-term considerations for Adoption</u>

- Intended use
  - *'Unidentified' opportunities for clinical benefit/use (e.g. arising from creative discussion with expanded audience)?*
- Drug description
  - *Modality, PPI, use in specific populations*
- Contraindications
  - *Destined for stand alone use or routine employment alongside/in combination (e.g. consider comorbidities)?*
- Testing
  - *Design in 'Resilience' (i.e. minimum service adaption to enable adoption and diffusion, regardless of context)*
- Regulatory
  - *Food and drug administration (FDA)*

This is a 'Live' document. The team may not know the answers to all questions at the start of the project. This will be refined and developed as the project progress.

Therapeutic Design & Development

UNMET CLINICAL NEED:

- As part of the TPP, comprehensively research and define the potential for benefit of the proposed therapeutic over current ‘standard of care’.

INTELLECTUAL PROPERTY:

- Engage with Business experts (i.e. UCLB) to ascertain if you have a novel invention, ensure freedom to operate and to protect foreground/arising intellectual property
- All researchers with potentially commercialisable research results should fill out a confidential Invention Disclosure form (IDF) and submit it to their UCLB Business Manager: http://www.uclb.com/for-researchers/do-you-believe-you-have-a-novel-invention/

Therapeutic Design & Development

PATIENT and PUBLIC INVOLVEMENT:

- Understanding the patient and clinician needs
  - Does your TPP meet all of the essential requirements expressed by frontline clinical care providers, patient and public contributors (PPI)?
- Research is carried out ‘with’ members of the public
  - Advisory members of a project steering group
- Early PPI engagement will help raise awareness of the therapeutic during development and potentially facilitate patient recruitment for subsequent clinical evaluation, possibly even financial investment
- Timely identification of future needs or opportunities

Therapeutic Design & Development

FINANCE:

- The development of small molecule compound to clinical level has significant costs that must be met.
- The TRO supports UCL PIs in attracting and managing public, commercial, investor and philanthropic funding for the development of small molecules and pre-clinical studies. These projects are then either spun out into a company or partnered with a pharmaceutical company, to help progress the project to clinical studies.
- Clinical studies need to be appropriately costed in partnership with the Joint Research office (JRO) or appropriate CTU.
- VAT needs to be added for manufacturing and/or services not resulting in a medicinal product.

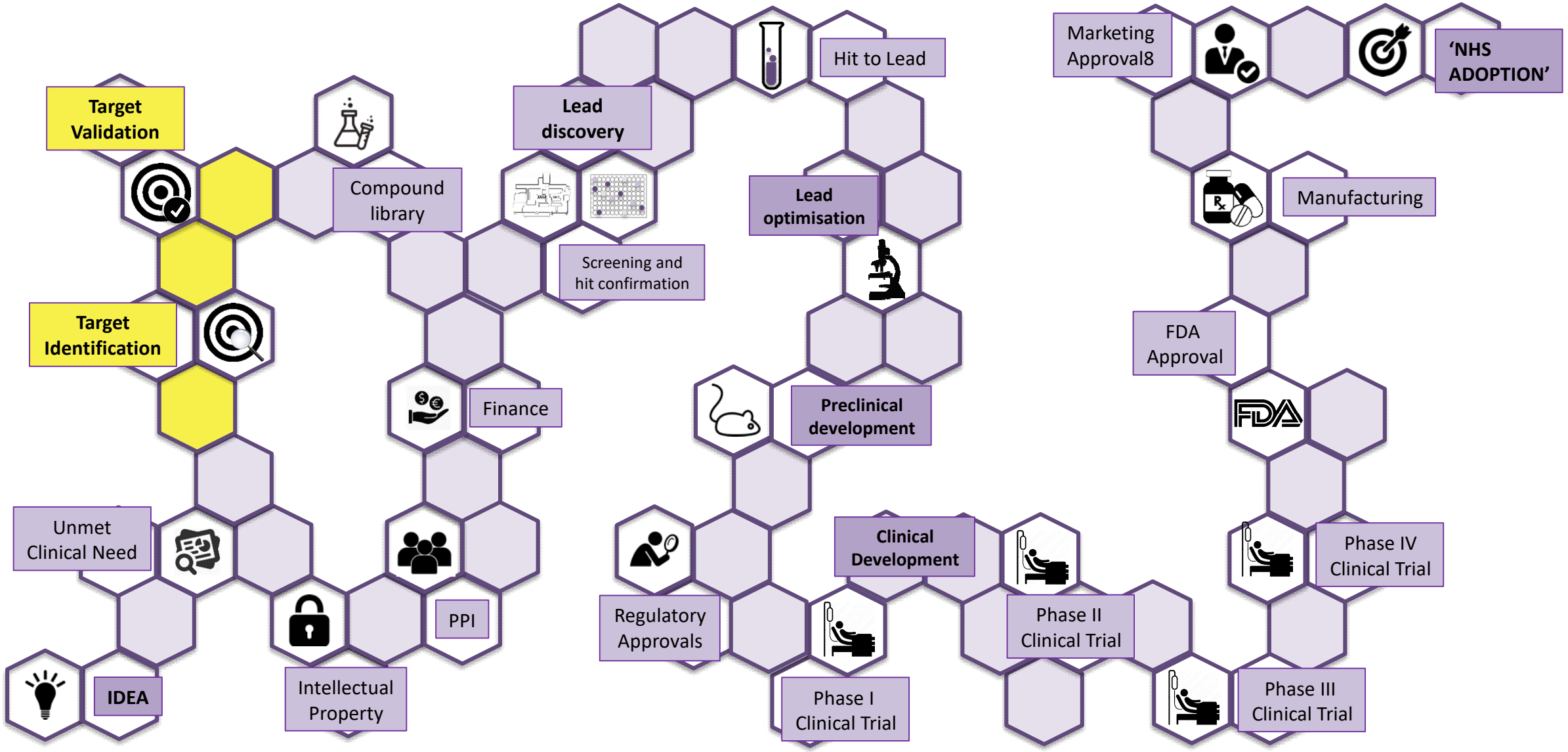
Therapeutic Design & Development

Small molecule Innovation Network:

- UCL and partner NHS Trusts are globally leading innovators in the discovery, design, development, screening, clinical delivery of small molecule drugs.

- UCL's Small molecule TIN spans multiple therapeutic areas, working across disciplinary boundaries and with our NHS partners to bring novel candidates to the market, and breathe new life into existing candidates through repurposing.

Work Flow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Target identifation and validation

Target identification

Identifying biological molecular structures which are ‘Druggable’. Druggable biological targets interact with the small molecule to change or alter the function of the target.

Properties of an ideal target

- The target has a pivotal role in the pathophysiology.
- The target expression is confined to a specific locations within the body.
- Enabled by a 3D model of the target for Druggable assessment.
- The target can be easily assayed in an high throughput screen.
- Regulation of the target by a small molecule has a favourable toxicity profile and potential side effects can be predicted using phenotypic data**.**

Approaches to target identification include:

- **Phenotypic screen approach**
- **Genetic association studies.**

Target identifation and validation

Target Validation

A prospective drug target has to undergo many validation experiments to show that it is directly involved in the pathway and that it will have a therapeutic effect.

How to validate a target?

- **Druggability assessment** – This involves exploring the sequence- related properties of the proteins and the 3D-sturucture using x-ray crystallography.
- **Assayability assessment** – This is to help with future compound screens. Biochemical and cellular assays need to be developed to enable the search for small molecule modulators of the protein.
- **Genetic assessment** - This involve looking at the genetic sequence and patient genetic material, which may predict efficacy of a potential therapy and predict potential adverse side effects. Targets may be expressed in different organs and even possess different functions dependent upon locations. So it is important to know the expression profile of the target from human genetic data as it confirms that the target is implicated in the disease and this can be replicated in animal models.

Target identifation and validation

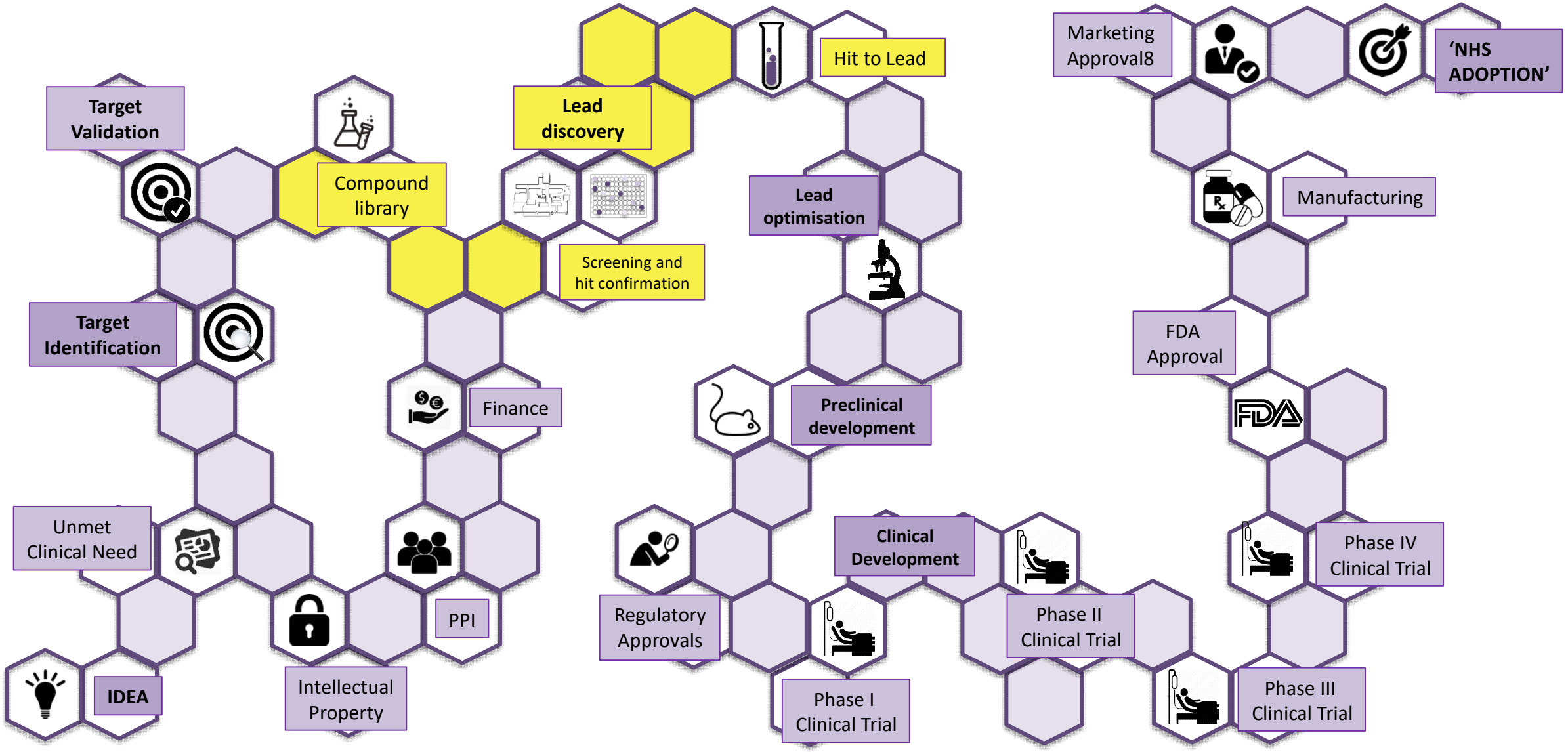
Assay validation

After identifying a target, a simple experiment to analyse enzyme activity or cell phenotype must be generated to screen against a small molecule library. This 'Primary assay' will be used to screen as many compounds as possible – potentially millions – so must meet a assay validation threshold before being used.

- **Primary assay –** This could be either a biochemical or cell based assay depending on the targeted disease. The assay would need to be HTS compatible – meeting the following criteria: potential for 1536-well plate format, demonstrable assay quality measures (assay window and robustness), known enzyme kinetics and reaction kinetics, demonstrated reagent and signal stability, DMSO tolerance, relatively inexpensive.
- **Othorganol assay –** A second assay that is performed after the primary assay, using an alternative substrate or technology platform. It is used to triage primary assay hits and remove false positives. 384-well format and can be more expensive as screen will be smaller.
- **Target engagement assay –** An assay to measure the extent to which the small molecules bind to the desired target. Depending on the available technology this strategy may be used as a Primary assay or on fewer compounds following triage of hit compounds.

The TRO Drug Discovery group at UCL can help generate HTS compatible assays.

Work Flow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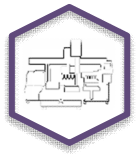
Lead discovery



Once a target is known and an assay for activity has been developed, the medicinal chemist search for compounds that can potentially interact with the target. As better compounds are identified they will then under go testing in various biochemical or/and cell based assays. The first step is to find a 'hits' which means, a poorly optimised compounds that nevertheless specifically interacts with the target. The ways of finding Hit compounds are:

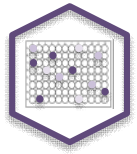
High Throughput Screen (HTS)

In an HTS large numbers of compounds (sometime many millions) are tested at a single concentration, searching for anything that appears to interact with the target protein**.** The HTS assay will require optimisation and miniaturisation as HTS screens are very expensive. Typical screening plates now have 1536 wells per plate. This means HTS allows for a high speed evaluation of many compounds usually in a highly automated fashion.

Once the 'hits compounds' that are found, their activity will be checked at multiple concentrations, a dose response. Activity may be confirmed in an orthogonal assay to eliminate false positive compounds that might have been identified as a result of interfering with the screening technology rather than directly modulating the function of the protein.

The generation of dose-response curves allows rank ordering of hits through the estimation of half maximal inhibitory concentration (IC_{50}) in case of inhibitor and half maximal effective concentration (EC_{50}) for measurement of other effects.

Lead discovery



Fragment-based screening

This is an alternative way of screening. Here libraries of very small molecule (molecular weight typically below 300) are evaluated at a high concentrations using highly sensitive biophysical technologies and the hits are identified, even if they bind very weakly to the target.

Virtual screen

If HTS or fragment screens are expensive to run an alternative approach could be a virtual screen. A virtual library of compounds can be docked *in silico* to a 3D model of the target to prioritise a small set of compounds for subsequent screening in a biochemical/biological assay.

Hit confirmation

Once a hit is identified, routinely a counter screening, target engagement assay is developed and executed. This confirms the ability of the compound to directly interact with the target protein. Hits may be further triaged to remove examples that interact with closely related biological targets and whose binding might cause confounding biological consequences.

Usually the range of potency of the hit against the target is 1µM to 50µM (100mM-5mM if a fragment).

Lead discovery

Hit to leads

Hits compounds are refined into a short-list of Leads compounds depending on:

- Synthetic accessibility
- Potency
  - Dose response
- Specificity
- Selectivity
- Non-toxic
- Drug-like structure
- Physical properties
  - Solubility
  - Lipophilicity
- Preliminary Structure Activity Relationship (SAR)

In lead optimisation the aim is to refine these properties to enhance~~d~~ required biological activity and reduce the potential for unwanted off-target side effects

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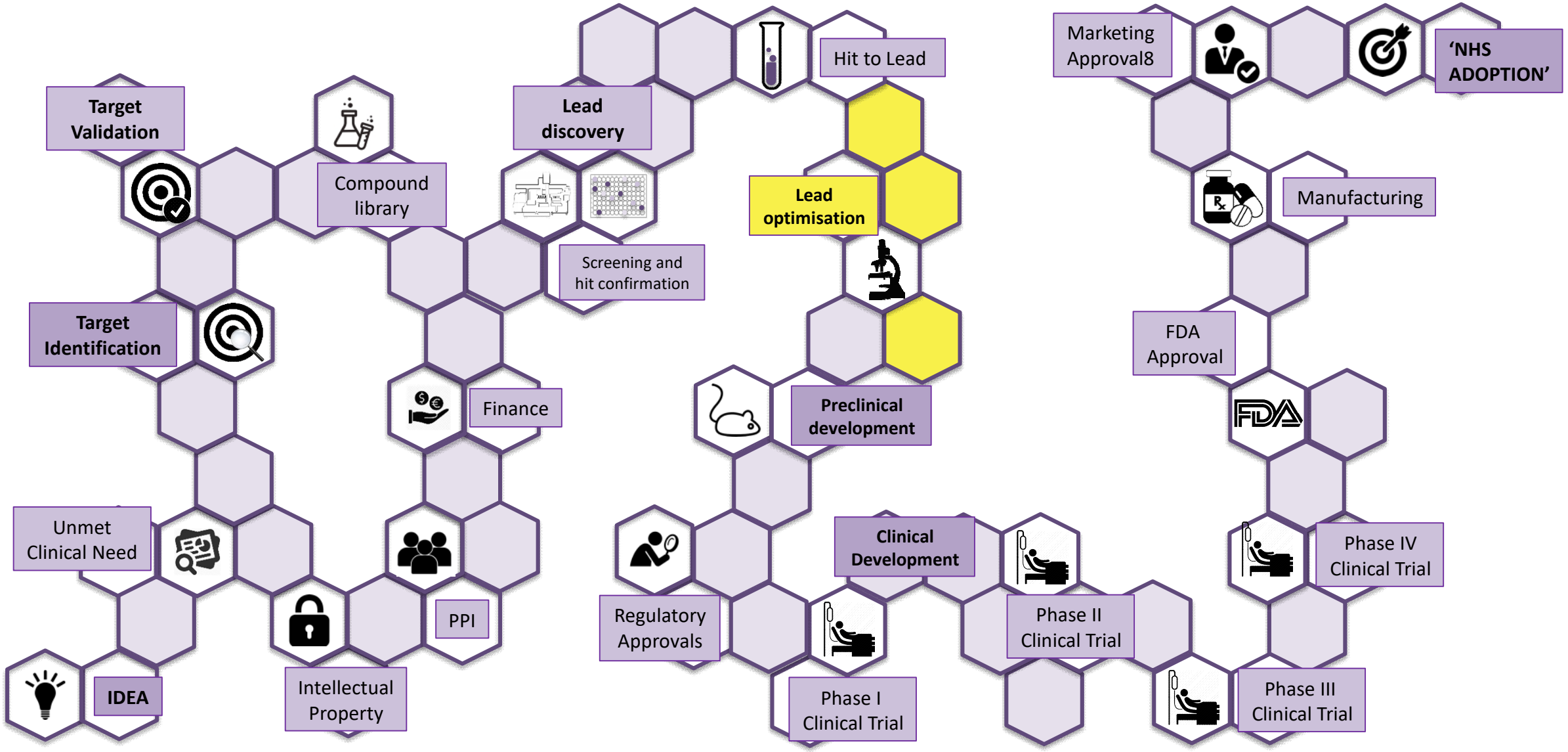
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Lead optimisation

During this phase of drug discovery, the aim is to enhance the lead compounds by making closely related compounds and evaluating their effects on *in vitro* systems on various biological properties. The aim is improve biological activity, target selectivity, potential for toxicity. Finally the compounds will be evaluated for how they are absorbed, distributed, metabolised and eliminated when dosed in an animal model of disease. Additionally the efficacy of the compound to modulate the disease will be evaluated in the animal model.

Physiocochemical

Control of physicochemical properties of the lead compounds is essential to speed the identification of potential drug candidates.

As a shorthand, medicinal chemists focus on compounds within the following boundaries. Compounds within these ranges have an improved likelihood of being orally absorbed and hence increasing the chances of successfully identifying a drug molecule. The Lipinski rule is;

- Its molecular mass is less than 500 daltons
- Its logP, which is a measure of lipophilicity, is less than 5
- The number of hydrogen bond donors is less than 5
- The number of hydrogen bond acceptors is less than 10

Lead optimisation

Solubility

Compounds should have sufficient solubility to enable easy formulation for future clinical studies. In addition to which, poor solubility makes evaluation of test compounds in vitro and in vivo models of disease difficult.

ADME

In vitro Adsorption, Distribution, Metabolism and Excretion (ADME) properties of compounds. These include permeability assessment in different cell lines such as colon carcinoma (Caco-2) cell line as a model for intestinal absorption, metabolic stability assessment using human liver microsomes as a predictor of how likely the molecule is to be removed by normal metabolic processes, and plasma protein binding assay which helps to understand key effects which drive drug potency in vivo.

Toxicity potential

Toxic potential of compounds is important to be check in the early stage of drug discovery. Therefore many in vitro assays have been developed to be use to measure the toxicity of a compound, many of which use human cell lines.

Lead optimisation

Pharmacokinetics

Pharmacokinetics in drug discovery is used evaluate how well an animal (as a model for human) might deal with a potential drug molecule. If the compound is poorly absorbed, highly metabolised or very difficult to formulate for evaluation it is unlikely to be a good candidate for testing in humans. Finally, the compound is screened in animal models of human disease for its efficacy.

Building SAR profile

By observing how small changes in chemical structure can change biological activity it is possible to understand which chemical groups in the drug molecule are engaging with the target. Hence, by building a structure–activity relationship (SAR) profile, predictions can be made with additional changes that might further improve the activity of the chemical series and so drive further optimisation.

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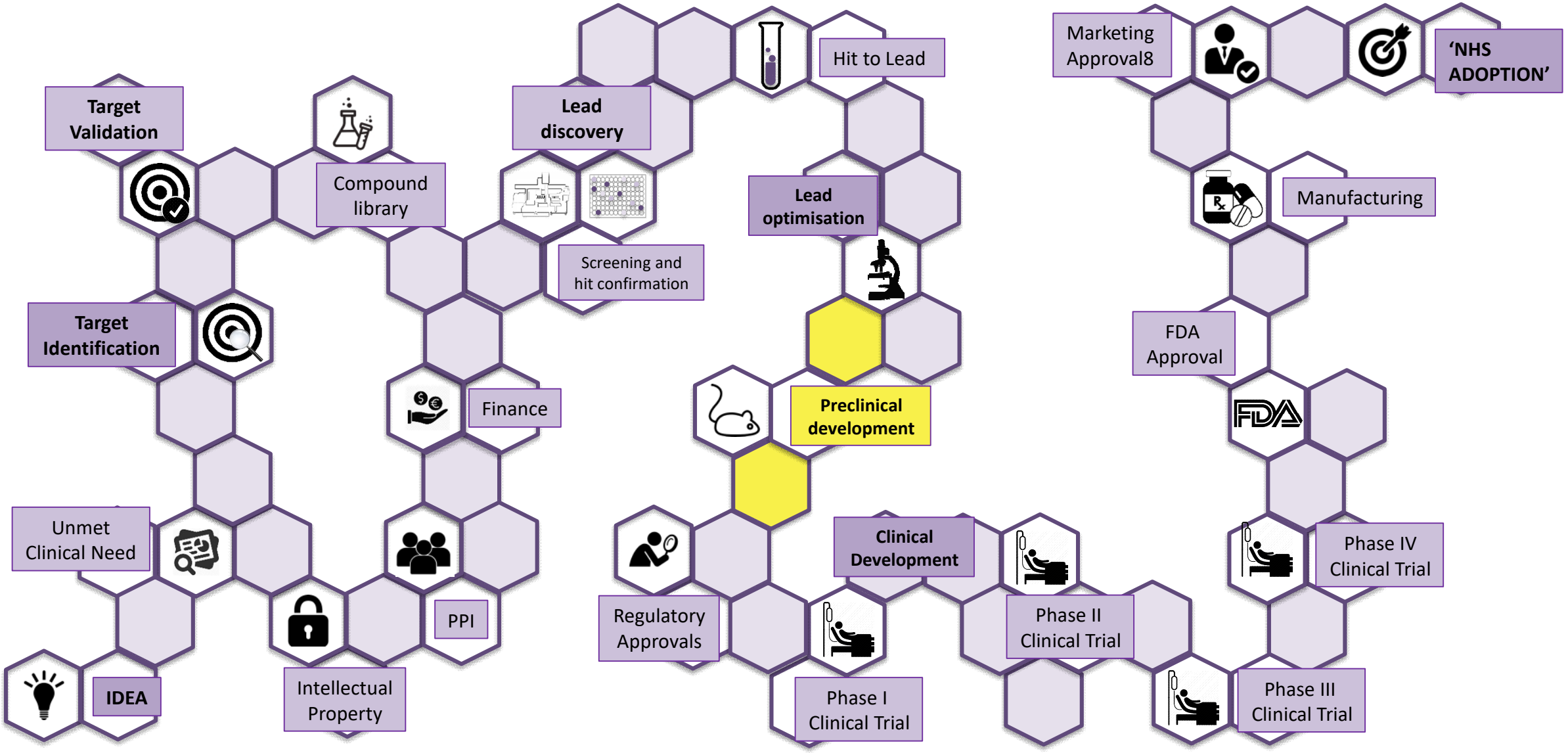
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Preclinical development

Millions of compounds may have been tested in the original screen, followed by as many as 500 compounds synthesised in the subsequent optimisation, leading to only 10-20 compounds being tested in advanced models of disease and finally, only 1-2 compounds selected for testing in humans. Those final candidate molecules needs to possess a well-define set of properties before they are considered suitable for testing in humans.

- **Chemical properties**: the compound should be stable and synthesis of the compound is straight forward so that it is easily scalable.
- **Physicochemical properties:** the compounds should be soluble and preferably meet the Lipinski 'Rule of 5'.
- **Pharmacological properties:** the compound should show selectivity towards the target and bind to the target, in both the *in vitro* experiments and the *in vivo* experiments (animal models).
- **Pharmacokinetic properties**: the compounds should be bioavailable, display appropriate half-life and the correct distribution in animals. The mode of action of the compound should be well known.
- **Safety and toxicity potential**: the compound should not show toxicity, such as cardiac toxicity, genotoxicity, and hepatotoxicity, in both in vitro or in vivo experiments.

When a compound passes all the necessary procedures, this compound undergoes Pharmaceutical formulation, which is the process where an active compound is combined with different chemical and/ or biochemical substances to produce the final medicinal product.

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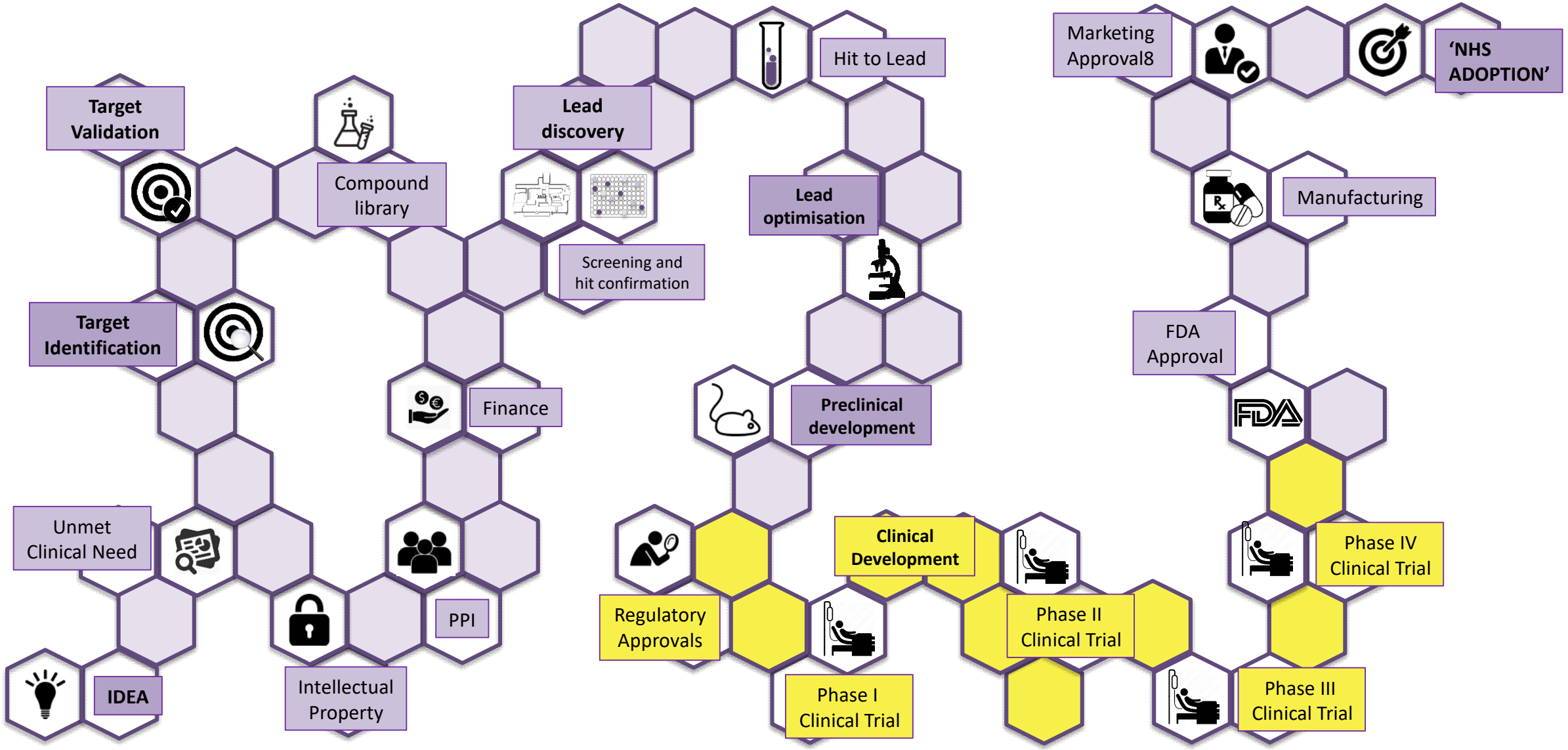
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Clinical development

Clinical trails

Once the preclinical compound is selected, the data is collated to support an approval of a Investigational New Drug (IND) application. This application is given to a regulatory body – The Medicines and Healthcare products Regulatory Agency (MHRA)/the Food and Drug administration (FDA) , so that the compound can move forward into human clinical trails. The application must include**:**

- Animal study data and toxicity
- Manufacturing information
- Clinical protocols for the proposed human trials
- Data from any prior human research
- Information about the principal investigator(s).

Only once the MHRA/FDA approves the application can the clinic trails begin. It is rare that the IND application are refused at this point but MHRA/FDA can suggest improvement. This is because a lot effort, time and money is used to get the compound this point.

The clinical trials are phased studies on volunteers to observe and collect data on the safety and efficacy of the compound.

Clinical development

Phase I

This phase of clinical trails are tested on approximate 10-100 healthy consented volunteers. This non- blinded trail assesses the safety and tolerability of the drug candidate, to determine any adverse effects. As well as this the pharmacodynamics and ADME are monitored, therefore observing the time it take for the drug to be metabolised and excreted from the body. Trials must be compliant with Good Clinical Practice (GCP).

Phase II

This phase of clinical trails are tested on approximate 50-500 patient expressing the targeted disease. These studies are carried out mainly to see the effectiveness of the drug in patients. Although other data can also be collected from this phase like studying the dose- response relationship and determine a dosing regimen. In addition the safety of the drug within these sets of volunteers are also monitored. This phase clinic trails are randomised and are either a single or double blind trail. Having controlled trails where a placebo is given instead of the drug in testing , helps compare the data.

Clinical development

Phase III

This phase of clinical trails are tested on approximate 500-3000 or more patients that have the targeted disease. These trail take place over many sites and over a wide verity of patients so that the results can be compared to existing treatment or standard of care of the targeted disease. As well as comparing the efficacy with other drugs and the effect of different dosage. The trails in the phase are more complex and require a lot of funding to be able to be carried out. These trails are randomised, controlled double blind trails.

If the outcomes from all the trails are positive, the data is then gathered and New Drug Application (NDA) is submitted to the MHRA/FDA for approve the licence of the drug.

Phase VI

This is where the follow up studies are carried out, to detect unusual or long- term side effects across a large population to look for patterns**.**

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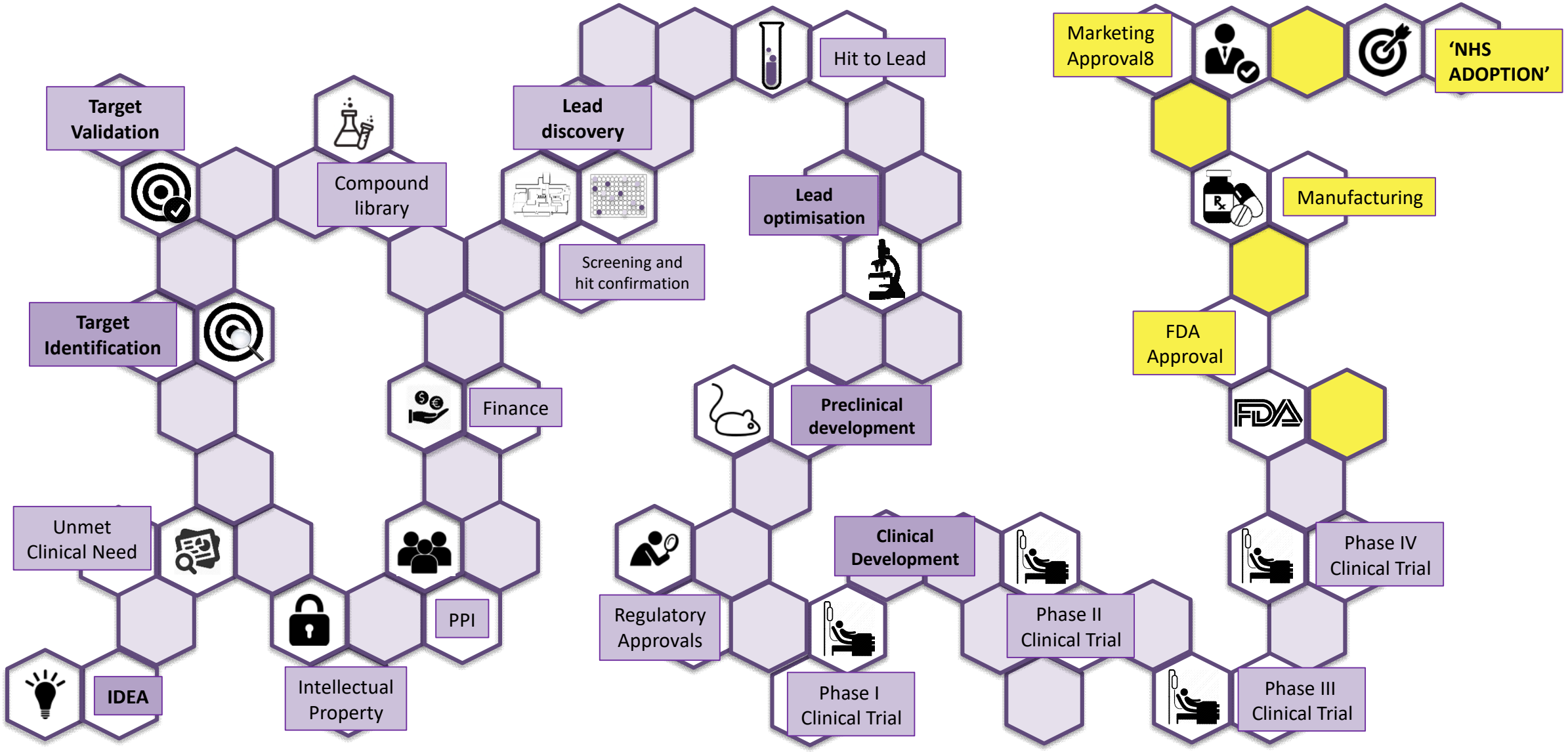
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Commercial adoption

Review, Evaluation and MHRA/FDA Approval

- Once the drugs is effective in clinical trails, the data is gathered and NDA is submitted to the MHRA/FDA for approve the licence of the drug.
- The regulating body will review and evaluate the safety and efficacy from all the data provided. If the benefited of the drug out weights an risk that arise, the drug will be approved.

Manufacturing and post-release monitoring

- The Pharmaceutical company will produce the drug in large quantities and available for patient use.
- Marketing approval needs to be obtained
- The drug is given to the patients and they are monitored to look for any adverse effect that may not have occurred in the clinic trails.

Commercial Adoption
- *NHS uptake*

UCL has implemented and is growing strategic platform partnerships to facilitate the accelerated development, commercialisation and adoption of therapeutics into the NHS

UCL TRO

UCLB

BRC's

UCLPartners
Academic Health Science Partnership

- Project management
- Regulatory advice
- Business Development
- Industry
- Clinicians & clinical delivery experts
- Clinical trial units
- Research & Development
- Patients & Public

UCL's Translational Research Office (TRO) builds on an increasingly vibrant translational culture across the wider university community by providing integrated support for translational research and industrial partnerships:
www.ucl.ac.uk/translational-research

Commercial Adoption
- NHS uptake: Key tips to facilitate adoption

DESIGN FOR MARKET:

- Continuously undertake internal and external stakeholder review of the small molecules:

  - The Steering Committee should meet regularly (at least every 6 months)

  - Ensure the identification and measurement of tangible data that will support adoption (e.g. outcomes meaningful to ward managers, hospital laboratory managers)

- Be mindful of the key 'facets' developed for successfully adopted :

FISCAL OPPORTUNITY	*- Clearly defined & attractive market potential*
SYSTEM OPERATIONS	*- Awareness & solutions to operational challenges of delivering the healthcare*
COMMUNICATION	*- Effective publicity of the biologic throughout its lifetime*
HUMAN FACTORS	*- Minimized use-related hazards, risks & inconvenience wherever practically possible*
PROOF	*- Provision of 'work as done' evidence (i.e. in both clinical & laboratory scenarios)*
IPR	*- Secure intellectual property rights as early as possible, then drive for market adoption as soon as possible*

Key contacts for support

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www.ucl.ac.uk/translational-research/

Small Molecule Innovation Network
www.ucl.ac.uk/slms/ovph/TINs

Research Services
www.ucl.ac.uk/finance/research/rs-contacts.php

UCL Business
www.uclb.com/for-researchers/

Joint Research Office
www.indigo-sandbox.ucl.ac.uk/jro/contact-us

UCL Partners
https://uclpartners.com/contact-us/