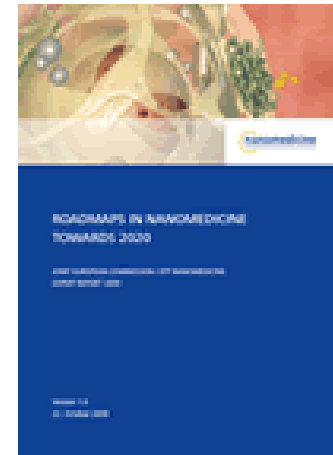


What does Healthcare Translatability mean for Nanomedicine– and whose view counts?

Peer Review is only part of the process and will not help stakeholders, unless applied research is translatable and of global originality

Mike Eaton

www.etp-nanomedicine.eu



Industry is only the messenger!

Radical Innovation

Radical Innovation

Innovative

Innovative



Healthcare is different
It is **Regulated**

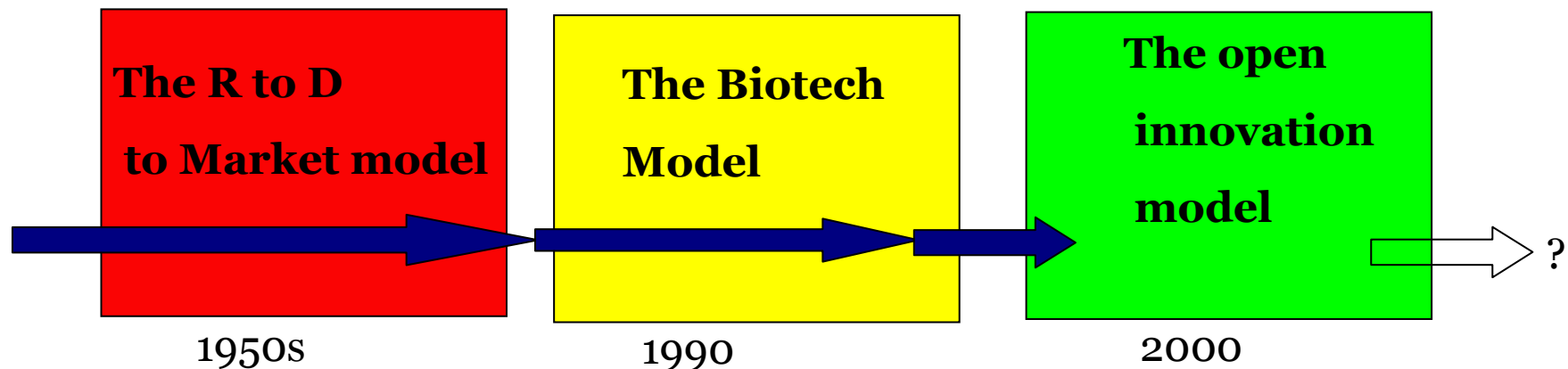
The regulatory and reimbursement processes **must** be seen as limiting academic freedom **not** industry.

Why is applied academic healthcare research funded?

- Training
- To help patients
- To help the economy
- To have a strong academic sector

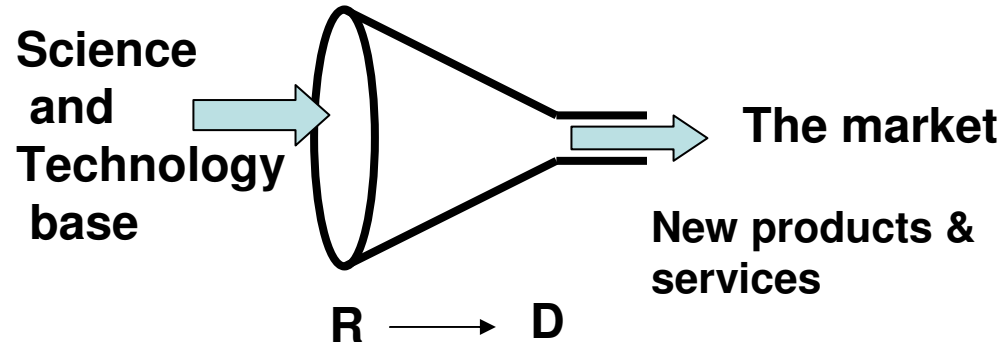
Corporate Organisations are changing

- Core competency praised in 90s
- Companies can no longer base themselves on a few competencies
- Traditional companies grow by efficiencies
- Knowledge architecture is more important than knowledge which is freely available

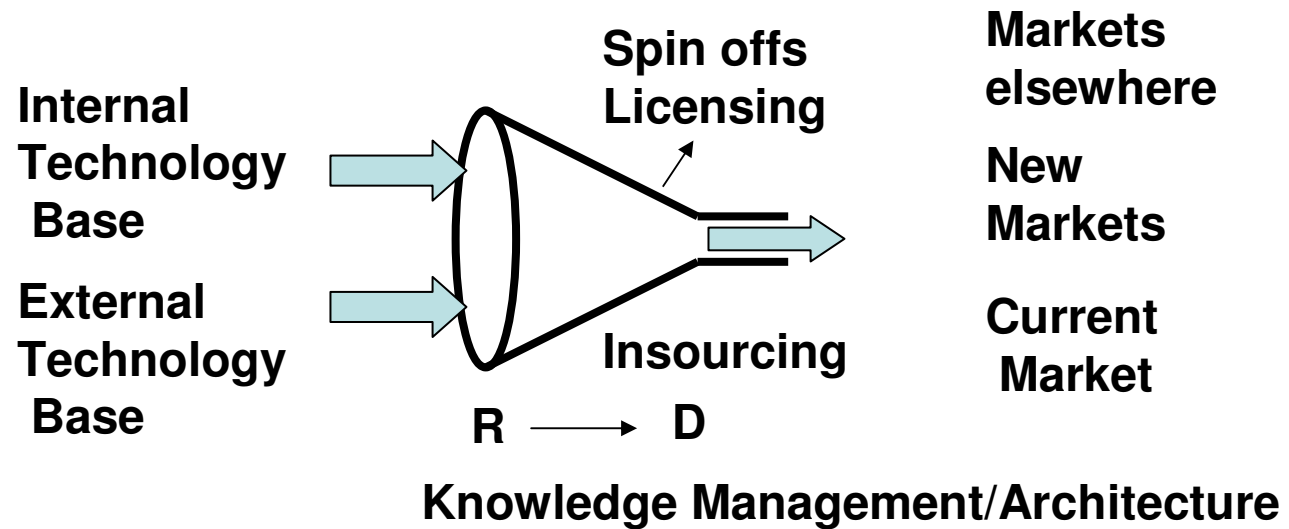


Greater use of outsourcing - Changes

Closed Innovation



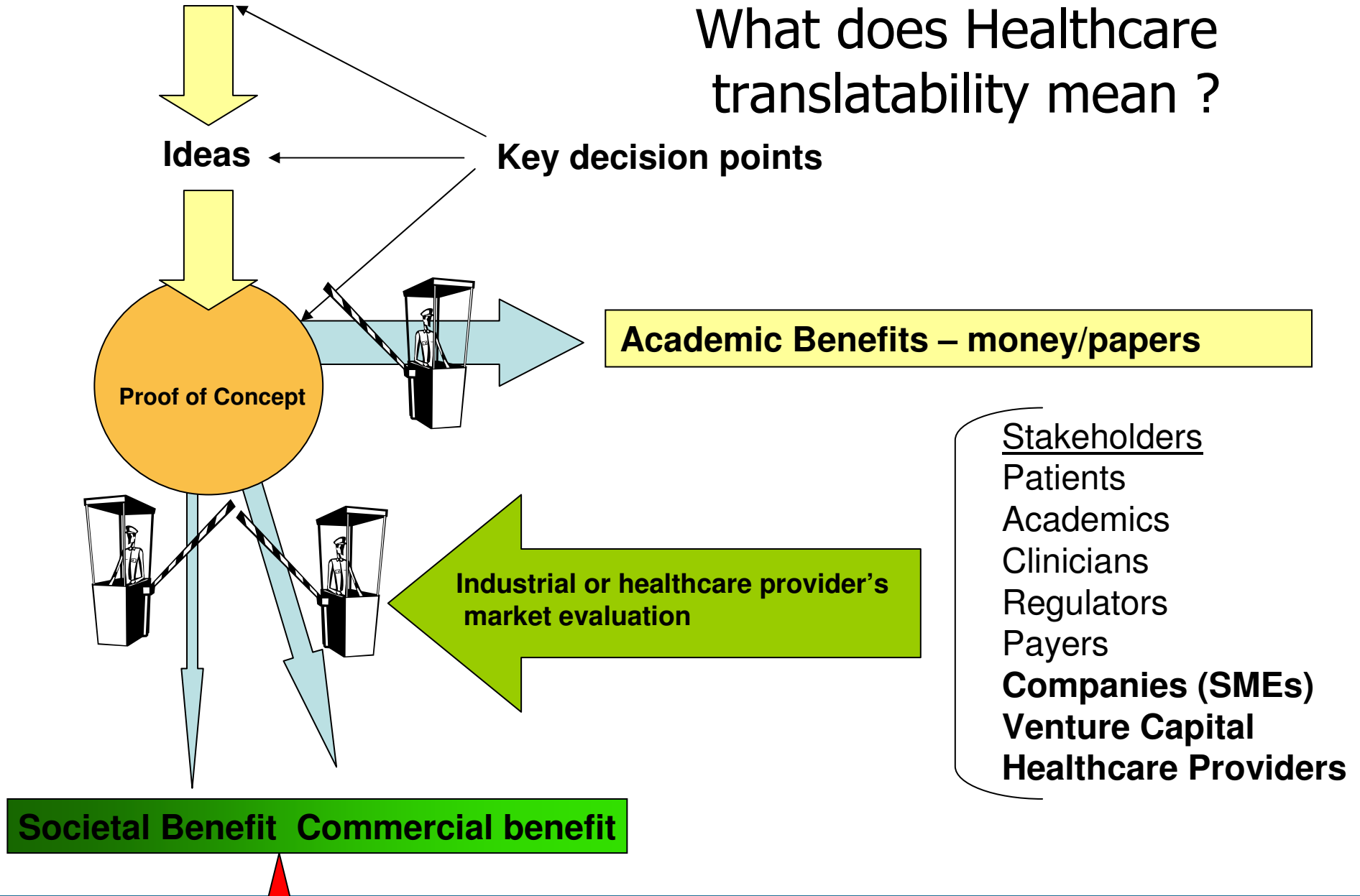
Open Innovation



What is special about Nanopharmaceuticals?

- New cohort of academics engaged –
No experience of working with Pharma - or wanting to do so in some cases?
- The majority of nanopharmaceutical academic output is non-translatable – low industrial interest
- Industry is looking for new technologies
- The “rules of engagement” here are not special to nano
- There are no published translatability rules - much is industrial know-how

What does Healthcare translatability mean ?



Peer Review is only one element..... Impact

Getting Quality & Innovation	Strategic area selection	Selecting Quality	Ensuring result
Environment	Choice of research area	Peer Review	Project Management
Industrial contact, needs and communication	Laissez-faire	Assessment criteria - Societal benefit or marketable (profitable) in current pharma climate	Access to state of the art manufacturing expertise at key steps. This may not be available in academia or contract research organisations.
Novelty of Science	ETP Roadmap	One off or strategic choice	Industrial and VC guidance
Industry know-how/ access	Industrial priorities	Majority decision good	
Breadth of expertise in academic facility	Checklist <ul style="list-style-type: none"> • Patient Impact? • Clinicians • Regulators • Manufacturing • Safety • Analysis • Reimburseurs • Industry – Is it profitable? does it matter?! 	Assess safety, healthcare impact & industrial relevance	
Patient/clinical input		Capable knowledgeable assessors	

1. Who are the Evaluators?

- Large Pharma

- Know the markets and regulations
- Monitor and evaluate global innovation
- Have knowledge of industrial literature and experience
- May not be so good with radical innovations but will know the questions to ask
- Innovation hungry

- SMEs

- Often do not understand the market or the position of the technology in the overall process

2. Who are the Evaluators?

- **Venture Capitalists**
 - Willing to take up a concept early
 - Can call on expert commercial opinion

- **Healthcare Providers**
 - Interested in Societal benefit
 - Non-commercial therapies
 - Not aware of the commercial world but often able to call on it

2. Who are the Evaluators?

- Academia

- Have a brief to explore frontiers of science, disruptive technologies
- Often have limited access to criteria for translatability
- Limited training for open innovation
- Limited to small networks and limited interdisciplinary activities
- Limited access to Safety and Toxicology

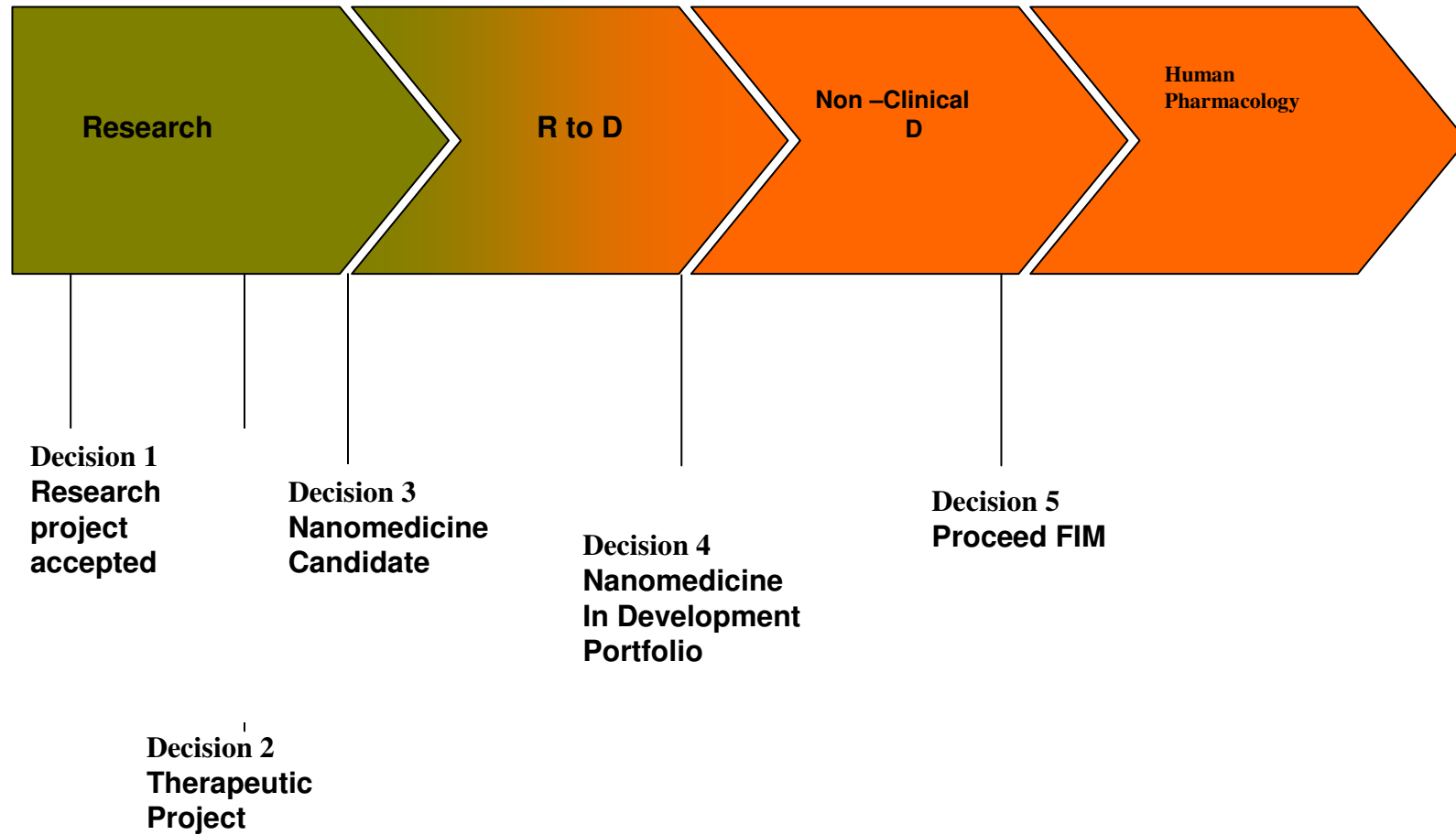
Open lists of company priorities and decision criteria
Large Molecules > Small Molecules

Blockbuster	Sales ~€1 Bn
Oral delivery of macromolecules	Dramatically increases sales
Intra-cellular access for macromolecules	Big increase in number of drug targets
Nucleic acid therapeutics	Delivery problems, Cost of Goods
CNS transport	Efficient delivery to CNS

Lists of company concerns and why- examples only

Photodynamic therapy	Niche Market with small patient numbers Not commercially attractive to large companies Not cost effective to improve?
Molecularly Imprinted Polymers	Cost and manufacturing issues
Boron Neutron Capture Therapy	History of Technical failure
Radioimmunotherapy	History of Commercial Problems
Gold nanoparticles	History of regulatory problems – Liver & Spleen retention
Polymer Therapeutics	Expensive for GMP manufacture. Immunogenicity and Pharmacology

Decision Points



Translatability Evaluation - Impact

These can be wrong or self fulfilling

(but should be listened to... even if only to ignore!)

1. Safety Evaluation – Does it do no harm?
2. Technical Evaluation – Is it manufacturable? What is it?
Pharmaceuticals? Stability?
3. Competitive Evaluation – Novelty?
4. Regulatory Evaluation – Meets standards for new drugs?
5. Reimbursement Evaluation – positive Cost / Benefit Analysis?
6. Commercial Evaluation – Profitable or Societal benefit or no value ?

RESEARCH DECISION POINT 1: 'RESEARCH PROJECT ADOPTED'

- Intellectual Property Department validates freedom to operate for the target entity i.e. concept lies outside existing patented property. **3**
- Definition of the **entity**, Nano-object, nanoparticle, nano-carrier **2**
- Biological rationale and its fit with the organisation's strategy **6**
- Early version of Target Candidate Profile (TCP) approved, including proposed competitive position **3**
- Technical and scientific feasibility assessment for *in vitro* / *in vivo* validation studies. **2**
- Basic DMPK. Is this concept likely to be acceptable to the regulators. Does it raise any safety flags? Are **all** (the constituents) of the nanomedicine **totally** cleared *in vivo* in an acceptable time or does the drug accumulate in any organ. Is the drug degradable *in vivo* and in the environment? Will it be harmful? Are there quantitative assays available for the entity and its possible metabolites? **4**
- Basic Toxicology. Have the constituents been assessed for potential pharmacological or toxicological effects? Will it be harmful? **1**
- Financially is this therapeutic likely to be viable and reimbursed? Is there a significant unique selling proposition (USP) over competitors such that it can compete and be reimbursed? **3, 5**
- Is the projected Cost of Goods of the therapeutic acceptable? Clearly the therapeutic dose determines the cost but as a rule of thumb once COGs get >\$100 / gm or monthly treatment costs of >\$1K then cost becomes an issue. **5, 6**
- Environmental impact . Does the material degrade in the environment or does it have no proven impact? **4**

RESEARCH DECISION POINT 2: ADOPT AS A THERAPEUTIC PROJECT

- Plan for transition from animal to human studies e.g. equivalent efficacy and toxicity **1, 2**
- Proof of Mechanism **2, 4**
- Proof of concept in disease model **2,3**
- Alternative nanomedicine structures considered, and a lead structure identified **2**
- Intellectual property patenting update **3**
- Nanomedicine delivery system –
Pharmaceutics/formulation considered **2**

RESEARCH DECISION POINT 3: 'APPROVE CANDIDATE NANOMEDICINE'

- Decision on precise structure of candidate **2**
- IPD updates patent situation. **3**
- At least one potential clinical indication **2**
- Non-human pharmacokinetics, disposition & efficacy (as appropriate); prediction of human pharmacokinetics and effective dose **4**
- *In vitro* and *in-vivo* activity demonstrated **2**
- Outline of manufacturing process defined **2**
- Outline of possible pharmaceuticals for this entity - formulation/stability **2**
- Confirmation of key analytical results to ensure manufacturability **2**
- Plans in place for non-clinical studies to support FIM (including toxicology plan) **1, 4**
- Translational Biology Strategy in place **2**

DEVELOPMENT DECISION POINT 4: ENTRY INTO DEVELOPMENT PORTFOLIO

- Project:
 - Full development team mobilised
 - TPP, Product Development Strategy created from TCP and Transition Strategy & Plan
 - Preliminary activities and resource plans
 - Updated research document summarising key data
 - IPD updates patent situation
 - Non-clinical package:
 - Toxicology package to support clinical plan
 - Single dose in vivo toxicology complete
 - Draft inputs to Investigator Brochure
- Technical: **2**
 - Development Process transfer report (or plans if not yet complete)
 - Development Process manufacturer selected
 - FIM formulation, Pharmaceuticals adapted to the nanomedicine
 - GMP manufacturing and technical transfer plans
- Clinical: **4**
 - Experimental Medicine Plan and first Clinical Development Plan, including budget & resources
- Regulatory Approval: **4**
 - Input to clinical plan
 - Regulatory strategy
- Commercial **5, 6**
 - Endorse TPP

DEVELOPMENT DECISION POINT 5: HUMAN PHARMACOLOGY STUDIES

- Project:
 - Updated/validated TPP
 - Updated/validated activities and resource plans
 - Updated document summarising data on Nanomedicine + “FIM package” document supportive for decision to proceed to human pharmacology testing
 - Risk assessment
 - FIM review of protocol
 - IPD updates patent situation
- Non clinical: **2**
 - Toxicology package (GLP)
 - Safety pharmacology package (GLP)
 - Multi-dose *in vivo* toxicology complete, plus additional safety studies required for FIM
- Technical: **2**
 - GLP released material for toxicology studies (same route as for human pharmacology studies)
 - 1st GMP batch
 - Secured supply for future GMP campaigns
 - Stability data available
 - Analytical qualification package complete
 - Product characterisation
 - Analytical support for GMP campaigns
 - Reference standard characterised
 - Preclinical and early phase manufacture
- Clinical: **4**
 - Updated clinical plan, including budget & resources
 - FIM protocol summary/ protocol approved by FIM reviewers.
 - Draft investigator brochure
 - Justification of starting dose in human and model of integrated pharmacology.
- Regulatory Approval: **4**
 - Regulatory overview
- Commercial **5, 6**
 - Revalidation of TPP

Industrial - Academic Symbiosis

- In Diagnostic sector (and electronics) good alignment
- In Nanotherapeutics poor alignment
- In Regenerative Medicine the indications are it will be poor?
- Why is thisSafety and Regulation? cf *in vitro* diagnostics

ETP N Output is Roadmap and some good input into calls

- Many projects are misguided but a few are outstanding
- ETP has provided guidance to academics. Scale of communication and lack of advisors in some countries.
- In general few have listened, except funders. A problem built up over decades. → Funding of non-translatable drug research.
- Why...the answers are in ETP report ...but due to researchers' lack of experience in the pharmaceutical sector
- Pivotal safety has been ignored as this is not necessary for publications, neither is it funded, encouraged, rewarded or requested
- Oddly safety of nanoparticles is often funded in a exposure rather than a patient context.

Some recommendations from roadmap

- **Public Authorities:**
- Improve industrial peer review of applied research proposals
- Where possible give a tranche of money to universities and ask them to invest it in their research as a portfolio. There would then be an incentive to choose and fund the best projects. Developmental Pathway Funding Scheme
- Request assessment of healthcare impact and industrial relevance in research proposals
- SAFETY first in research proposals – some success on this in Euronanomed
- **Industry**
- Increase the efficiency of industrial contacts with universities
- Provide detailed sources of information on industrial priorities
- Share specialised industry technologies and expertise
- **Academia**
- Exploit the expertise of experienced retired industrial scientists
- Train academics with an understanding of drug discovery
- Change the academic culture towards encouraging and rewarding real innovation and entrepreneurship in Europe
- Plug in to industry news-flows using widely available internet websites
- Understand the implications of the “Open Innovation” concept
- Change projects if not translatable!!! Or at least understand the barriers to commercialisation

Some Issues

- Limited number of accessible safety labs
- Some fields have grown for decades – without thought about translation – industry will not engage easily.
- Academics do not easily change fields but they will chase money
- Need for paradigm shifting research – not incremental
- History of lack of communication between Pharma and Academia, unlike diagnostics - mirrored with regenerative medicine
- Larger company guidance essential for EC
- Need to engage with best academics, this is also an industrial priority

The pharma sector is experiencing challenging times

- Globalisation and Generics are influencing strategy
- The role of the academic sector is important
- Best ideas are being sought globally
- This is a significant opportunity for the academic sector both in Europe and US
- Aim is win-win-win

Acronyms

- ETP European Technology Platform
- POC Proof of concept
- PK Pharmacokinetics
- IP Intellectual Property
- TCP Target Candidate profile
- FIM First (Time) in man
- GMP Good Manufacturing Practice
- CMO Contract Manufacturing organisation
- TPP Therapeutic Product Profile
- IPD Intellectual property department
- GLP Good laboratory practice
- EPR Enhanced penetration and retention
- NCE Novel Chemical Entity
- NBE Novel Biological Entity
- USP Unique Selling Proposition