Innovative Medicines Initiative

Delivery and Targeting Mechanisms for Biological Macromolecules

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Deputy coordinator: GlaxoSmithKline

Participating companies: Sanofi, GlaxoSmithKline, AstraZeneca, and Novo Nordisk

efpia

Innovation gap in drug development

- Increasing R&D expenditures
  - R&D costs have tripled during the last 15 years ($ 17 bn in 1996 → $ 47 bn in 2009)
- Stagnating output
  - Approx. 4,500 new molecules (900 in oncology) are currently being developed
  - Every year only approx. 30 new molecules are approved by health authorities

    (53 in 1996 → 24 in 2009)
  - Attrition rate of > 95%
- Limited drug target space
- Increasing generic competition

→ An environment ripe for change and opportunity

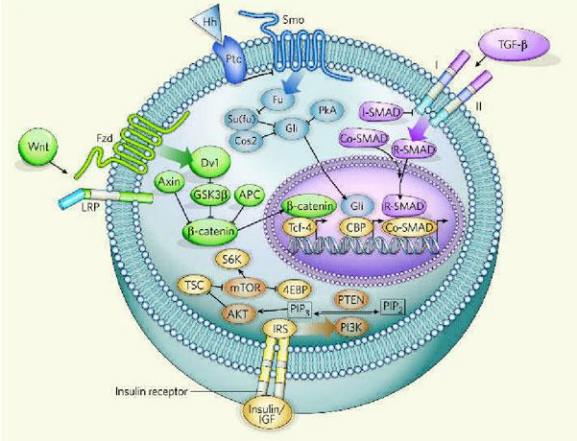
Source: PhRMA Outlook 2010 Report, FDA

Adapted from Service R.F.: *Science* 303, 1796 (2004)

Critical steps for innovation

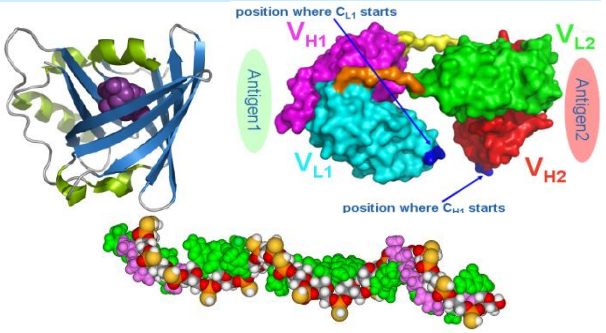
We know what to target → Therapeutic modalities → Translational medicine

- **Understanding disease**
- **New pathways**
- **Biomarkers**

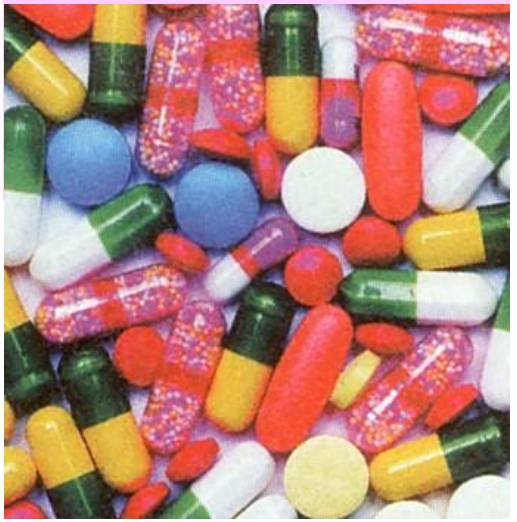


Adapted from Fishman & Porter: *Nature* **437**, 491 (2005)

- **Small molecules**
- **Biologics**
  - **Proteins**
  - **Peptides**
  - **Oligonucleotides**
  - **Therapeutic stem cells**

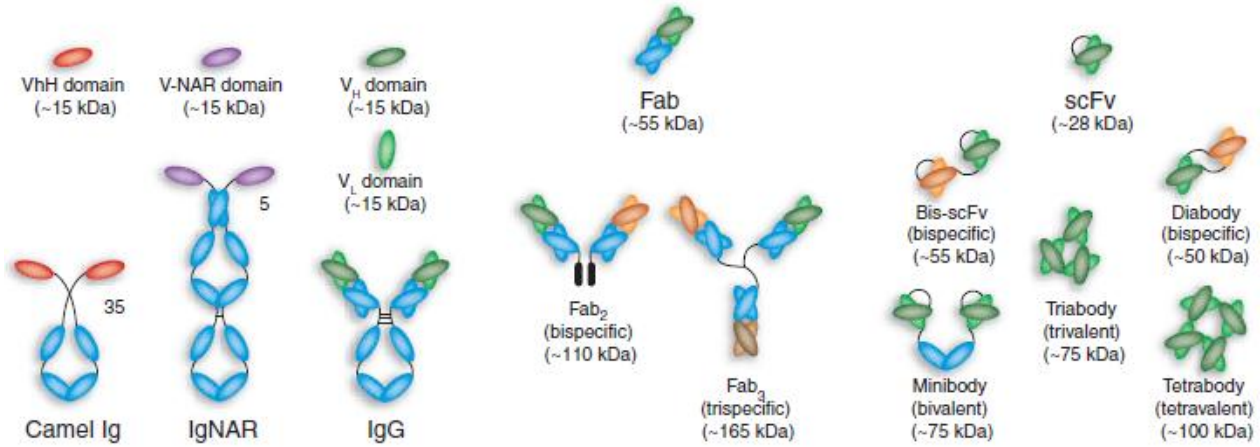


- **Pharmacology**
- **PoM**
- **PoC**



Novel biologics-based therapeutic modalities: Antibodies and scaffolds

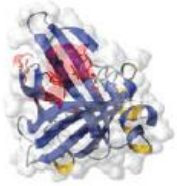
- Huge success of therapeutic antibodies
- Many new antibody formats in development



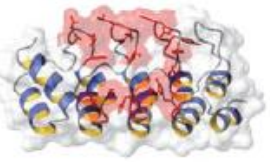
Adapted from Holliger & Hudson: *Nat. Biotech.* **23**, 1126 (2005)

- Alternative non-antibody scaffolds

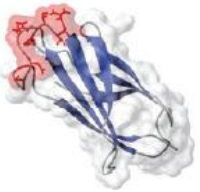
Anticalin (lipocalin)



DARPin (Ankyrin repeat protein)



Adnectin (fibronectin)

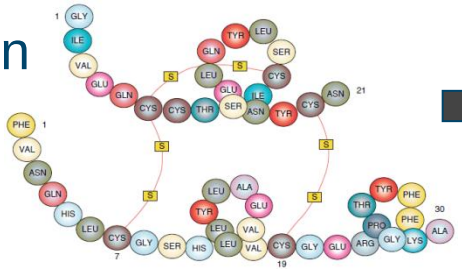


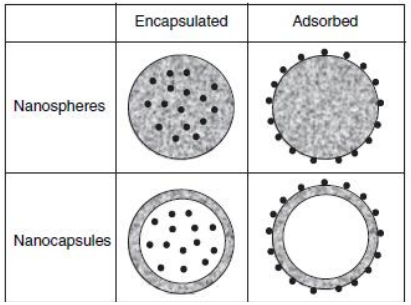
Adapted from Binz H.K. et al.: *Nat. Biotech.* **23**, 1257 (2005); Skerra A.: Curr. Opin. Biotech. **18**, 295 (2007)

Novel biologics-based therapeutic modalities: Oral peptides

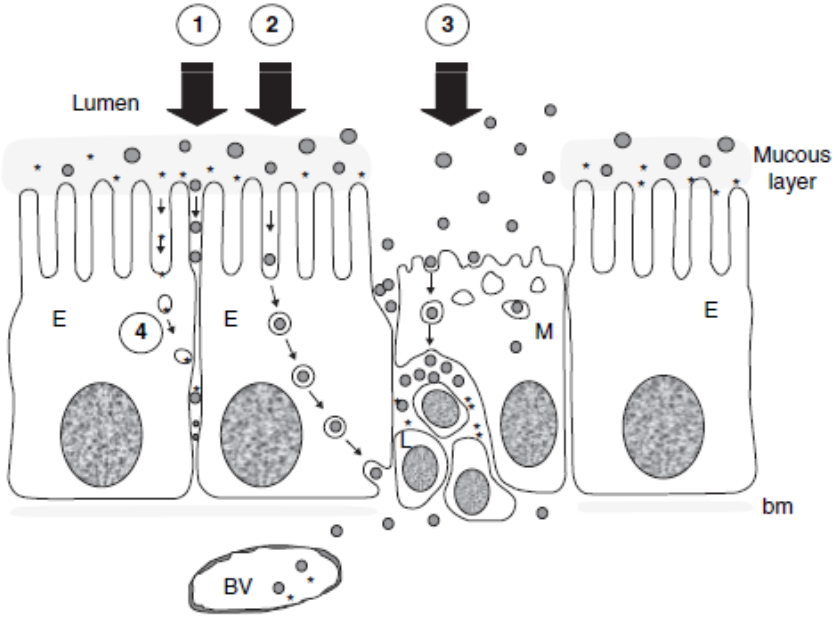
Example: Oral delivery of insulin

Insulin



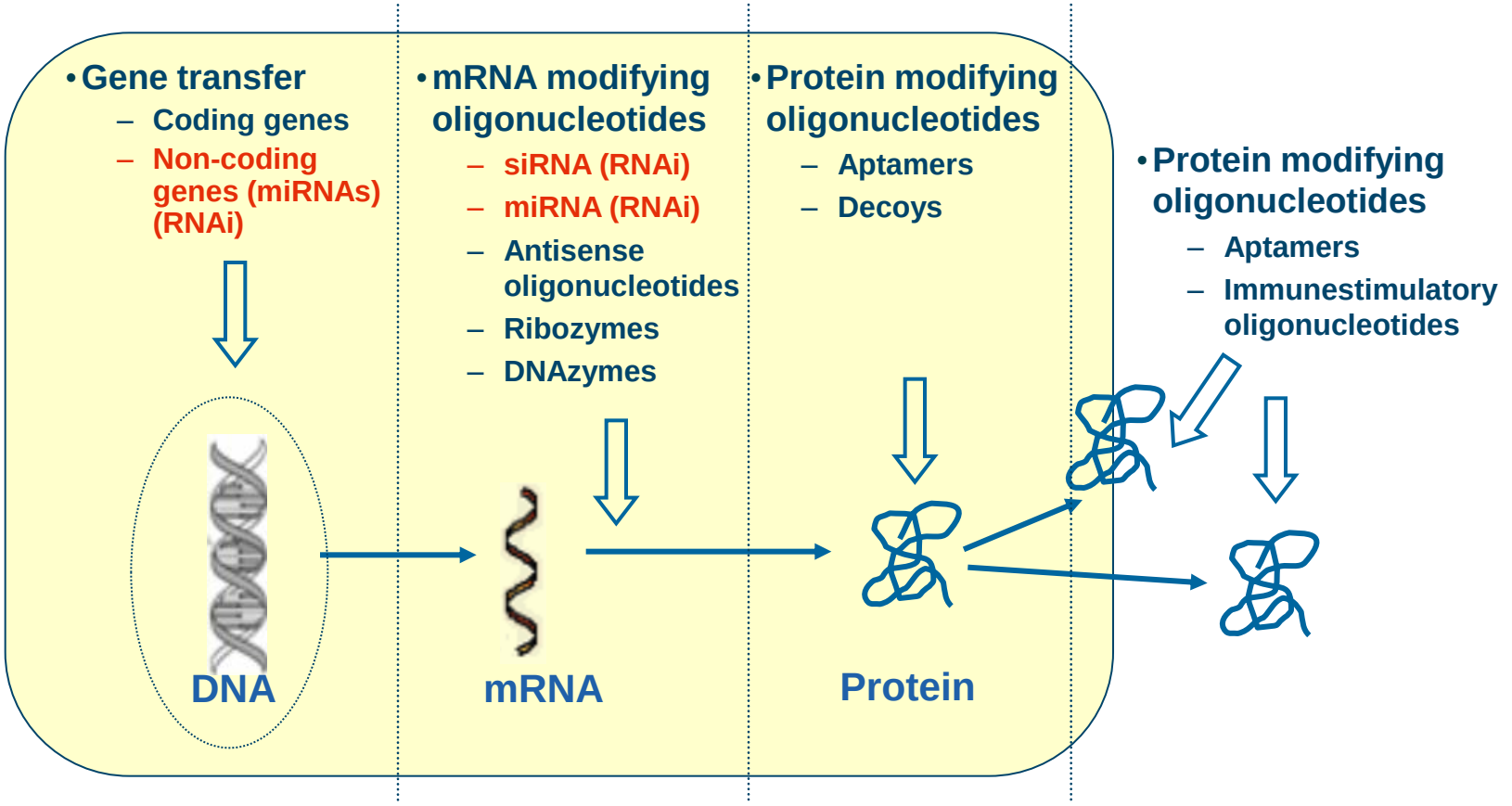


- **Generate insulin nanoparticles**
- **Transport across the intestinal epithelium**
  - **Paracellular**
  - **Transcytosis (enterocytes)**
  - **Transcellular (M cells)**
  - **Receptor mediated of free insulin**



Adapted from Damge et al: *Expert Opin. Drug Deliv.* **5**, 45 (2008)

Novel biologics-based therapeutic modalities: Oligonucleotides



Novel biologics-based therapeutic modalities: RNAi therapeutics

1.2% of human genome

Protein genes

RNA genes

Coding DNA

Non-coding DNA

Transcription

mRNA

miRNAs and other ncRNAs

Ribozome

RISC

RNA induced silencing complex

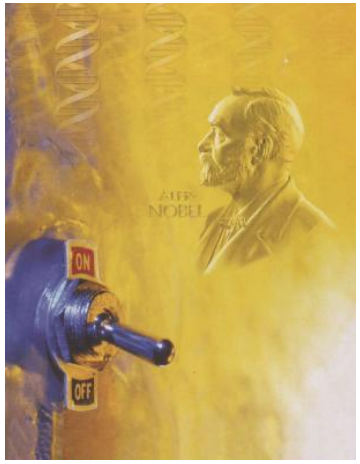
Translation

Protein

RNAi

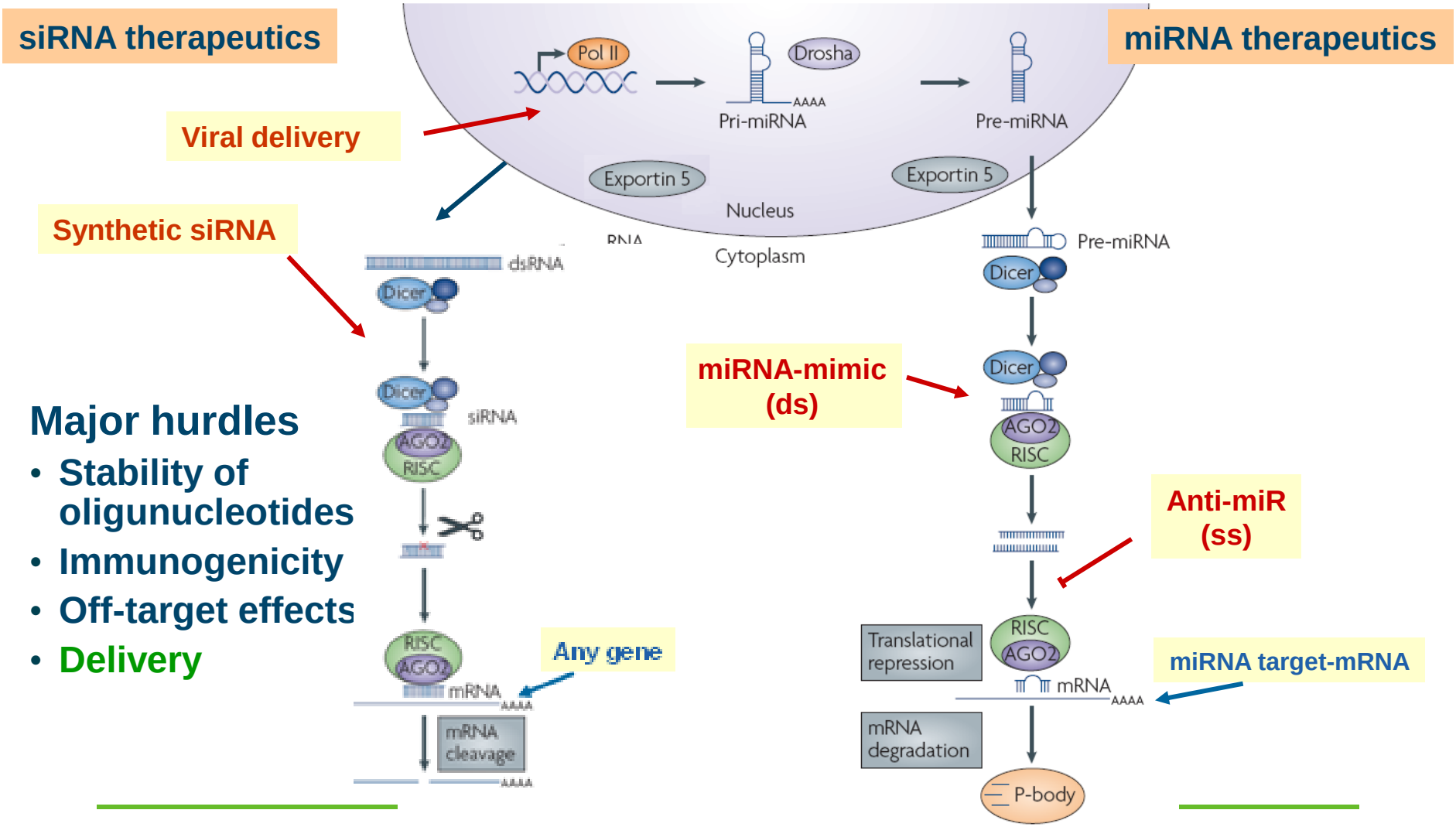
Translational repression or mRNA degradation

Cellular regulation



RNAi mediated therapeutic modulation by oligonucleotides

Novel biologics-based therapeutic modalities: miRNAs and siRNAs



Major hurdles

- **Stability of oligunucleotides**
- **Immunogenicity**
- **Off-target effects**
- **Delivery**

Adapted from De Fougerolles A. et al.: Interfering with disease: a progress report on siRNA-based therapeutics. *Nat. Rev. Drug Disc.* **6**, 443-453 (2007)

Common challenges of biological macromolecules

- Limited tissue accessibility
  - Limited delivery across biological barriers
- Poor delivery across cellular membranes
  - Restricted to extracellular targets
- Undesirable pharmacokinetic properties
  - Short half-life in blood
  - Rapid excretion
  - Reduced stability
- Potential immunogenecity
- Cost-of-goods affected by poor delivery properties

Objectives of the full project

- Improve understanding of intracellular uptake mechanisms of biomacromolecular drugs (proteins, peptides and oligonucleotides)
- Develop nanocarriers to deliver these new drugs
  - To and across epithelial barriers, such as
    - Blood brain barrier (BBB), air-blood barrier, blood-retina barrier, skin barrier, intestinal barrier
  - Across cellular membranes into target cells
- Develop nanocarriers for oral uptake of these drugs

Need for public-private collaboration

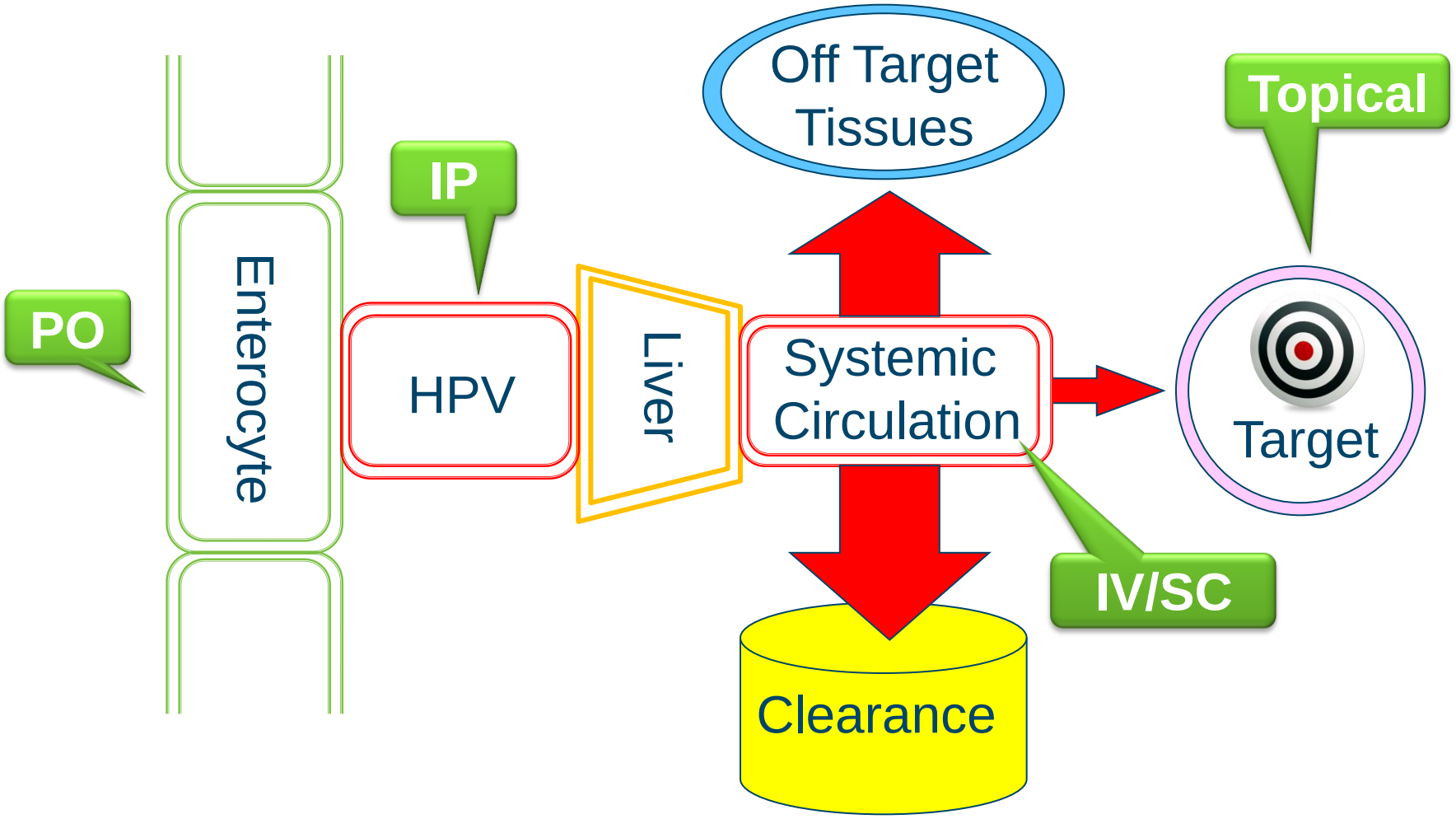
- Individual Pharma Companies tend to be **compound driven** with little scope for fundamental research
- The successful delivery of macromolecules in a clinical setting will require significant **tangential research** to provide platform understanding of the challenges
- This can only be delivered by a **cross-functional/ cross-institutional consortium** of academic, Small Medium Enterprises (SMEs), regulatory and industrial scientists

Suggested architecture of the project

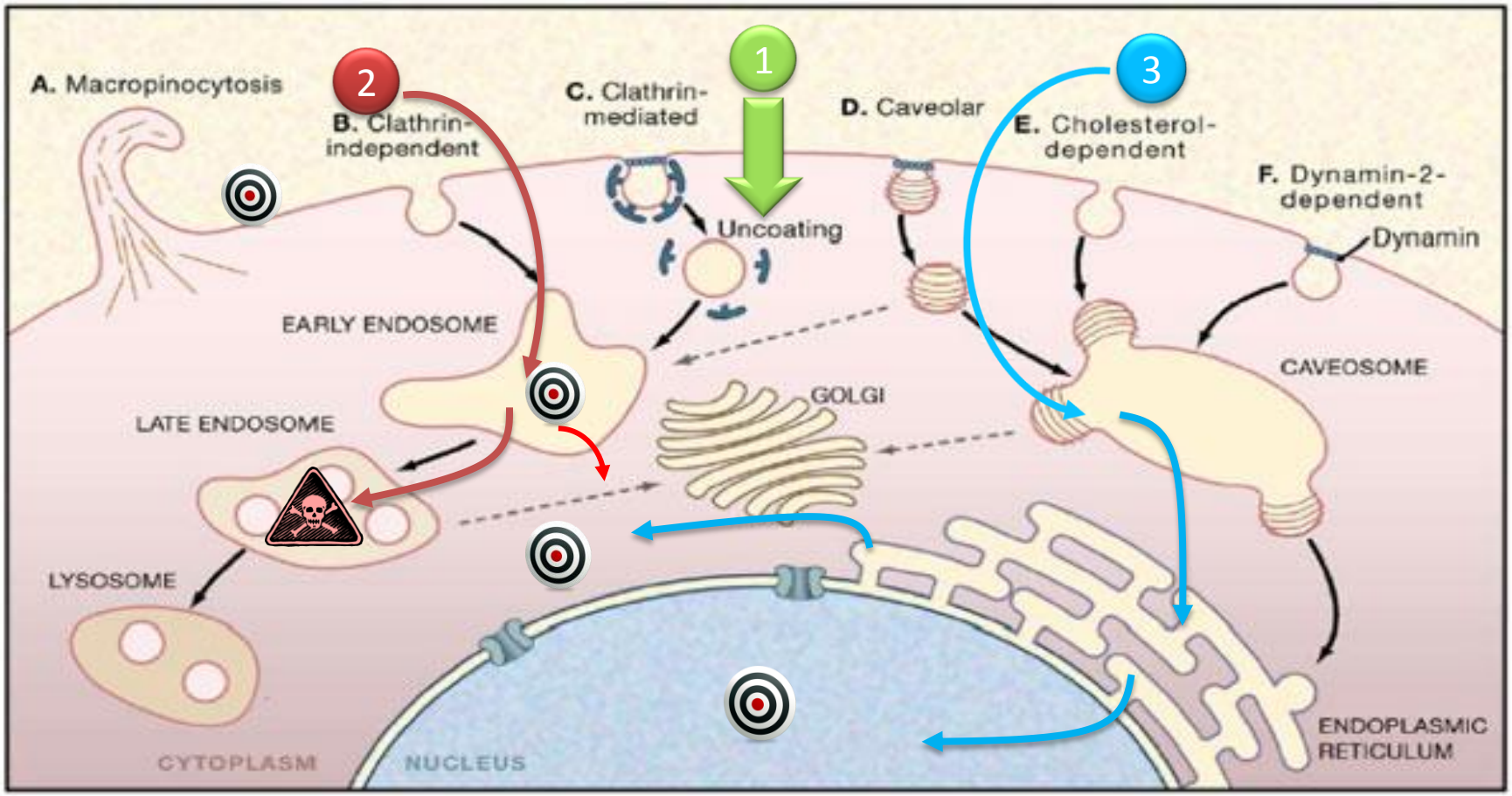
Proposed work package areas

- **Understanding** the mechanisms of uptake of biomacromolecules across **biological barriers**
- **Investgating** the mechanisms of **cellular uptake and sorting**
- **Novel approaches to delivery** of biomacromolecules across biological barriers and cellular membranes
- **Pre-Clinical and Clinical testing** of new formulations
- **Database** and analysis
- **Project Management**

Biological barriers to successful delivery



Cellular barriers to successful delivery



Adapted from Marsh and Helenius, Cell, 124, 729-40

Expected contributions of the applicants

- **Molecular and cellular biology**
  - Mechanisms of cellular uptake and intracellular trafficking
  - Imaging technologies for monitoring and quantification of cellular uptake and intracellular trafficking
  - Generation of *in vitro* and *in vivo* models for monitoring cellular uptake and intracellular trafficking
- **Nanotechnology / Formulation**
  - Protein and nucleic acid chemistry, e.g. for conjugation with targeting molecules
  - Generation of novel nanocarriers for delivery of biological macromolecules across biological barriers and cellular membranes
- **Manufacturing**
  - Combined payload and delivery system

Expected (in kind) contributions of EFPIA members

- **Project direct**
  - Supply of biological macromolecules as tool payloads (e.g. proteins, antibodies, oligonucleotides)
  - Testing of novel nanocarriers in disease-relevant *in vitro* systems
  - Pharmacological studies using nanocarriers in appropriate disease animal models to fulfil IND requirements
  - Design of prospective clinical trial(s): resources and expertise for trial design
  - Execution of prospective clinical trial(s) and interpretation of results: resources and expertise to conduct multi-centre clinical trials (monitoring, data management, etc.)
- **Support functions**
  - Project Management
  - Statistical Analysis

Pre-competitive nature

- **Basic research** in molecular mechanisms of cellular uptake of biological macromolecules, e.g.
  - Mechanisms to cross cellular membranes
  - Endosomal escape mechanisms
- **Basic research** in nanocarrier technologies
  - Share nanocarriers for delivery of competitive biological drug substances
- **Synergies** among protein, peptide and oligo uptake mechanisms
  - Similar size (>5kd), charge and shape

What's in it for you?

- **Directly Benefit Patients with your research**
  - Yor work will lead to better medicines
  - Targetting previously „undruggable" diseases
  - Facilitate the „Bench to bed-side" paradigm

- **Chance to be involved in a new environment for developing the next generation of drugs**
  - Be part of a pan-European network focussed on developing future therapeutic modalities in a pre-competitive environment
    - Access to academic expertise
    - Access to Pharma drug development capability
    - Access to IMI resources

Expected impact on the R&D process

- **Novel therapeutic opportunities**
  - Providing novel strategies to treat unmet medical needs
  - Expansion of drug target space
    - „Non-druggable“ targets
    - Pathways/networks of pathways instead of single targets
- **Strengthening of novel biological-based therapeutic modalities**
  - Improved delivery will increase the therapeutic index
  - Reduce effective doses required
  - Increasing investor confidence that new therapeutic modalities will deliver viable medicines

Novel Molecules + Improved Delivery = Better Medicines

Key deliverables of full project

- Elucidation of cellular uptake mechanisms of biological macromolecules
  - Proteins, peptides, oligonucleotides
- Nanotechnology-based delivery methods
  - Scalable chemistry of nanocarriers
  - Provide drug-like ADME properties to biological macromolecules
  - Cross biological and/or cellular barriers
- Delivery strategies appropriate for the clinic
  - Oral uptake, inhalation, topical
  - Injectable: I.V., subcutaneous, intra-articular, intra-thecal

Combine forces of industry and academia to generate the next generation of biologics-based medicines

Thank you for your attention

We make biologics happen!

Please address all questions through the IMI Executive Office

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