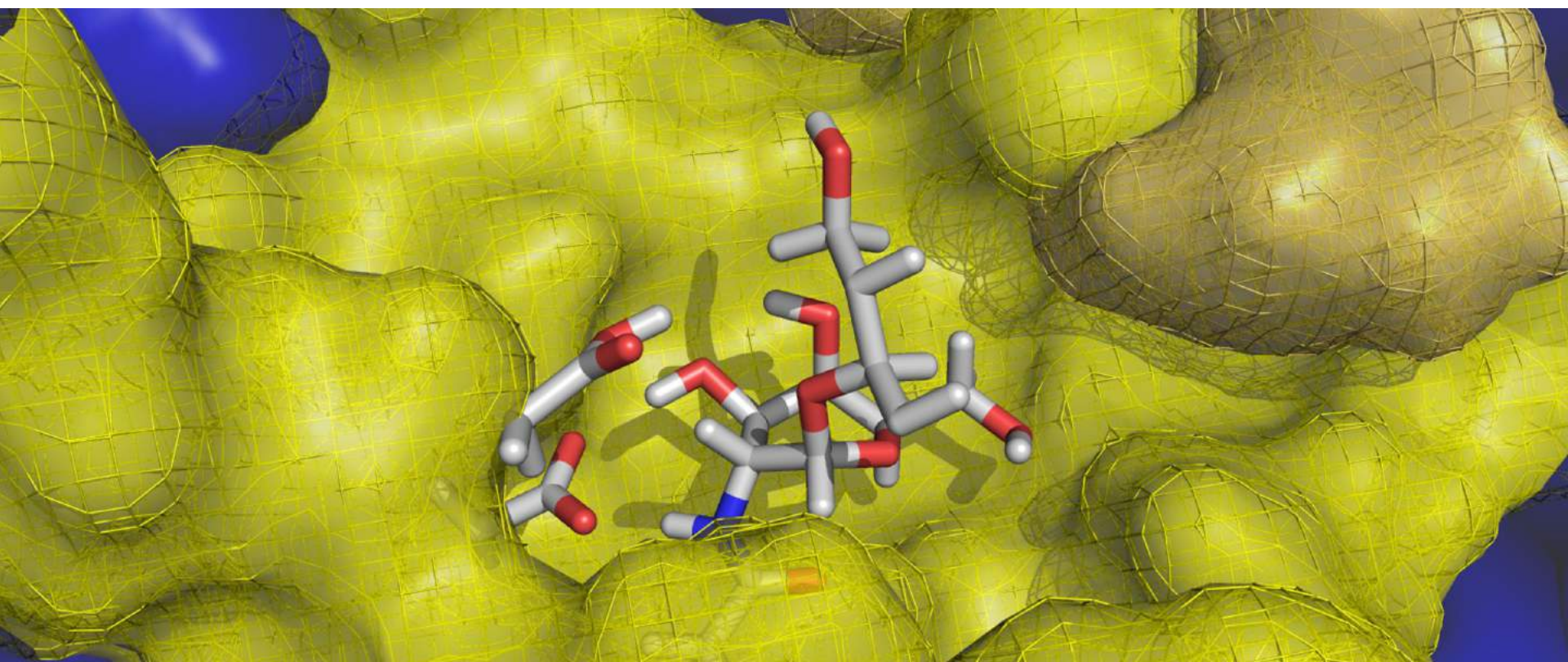


Drug Discovery – an Introduction

Pedro Alexandrino Fernandes
Department of Chemistry and Biochemistry
University of Porto
Portugal



Drug Discovery – an Introduction



What is a drug?

Drug Discovery – an Introduction



What is a drug?

A pharmaceutical drug can be loosely defined as any chemical substance, natural or synthetic, which when taken into a living body, affects its functioning or structure.

Drug Discovery – an Introduction



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A pharmaceutical drug can be loosely defined as any chemical substance, natural or synthetic, which when taken into a living body, affects its functioning or structure.

Pharmaceutical drugs are intended for use in the medical diagnosis, cure, treatment, or prevention of disease.

Drug Discovery – an Introduction



Drug Discovery and Development Pipeline

Drug Discovery – an Introduction



Drug Discovery and Development Pipeline

Target Discovery

Expression Analysis

In Vitro Function

In vivo validation;
(e.g. knockouts)

Bioinformatics

2-3 years

Drug Discovery – an Introduction



Drug Discovery and Development Pipeline

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Lead Discovery

Traditional Chem.
Combinatorial Chem.
HTS
Parallel Synthesis
Virtual Screening

1 year

Drug Discovery – an Introduction



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Medicinal Chemistry
Cell assays

**Structure-Based
Drug Design
ADME properties**

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Tests in animals
Clinical Trials
(I, II & III)

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U.S.A – FDA
Europe (EMA or
country-by country)
Japan (MHLW)
Rest of the world

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MARKET

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Total time ≈ 12-20 years

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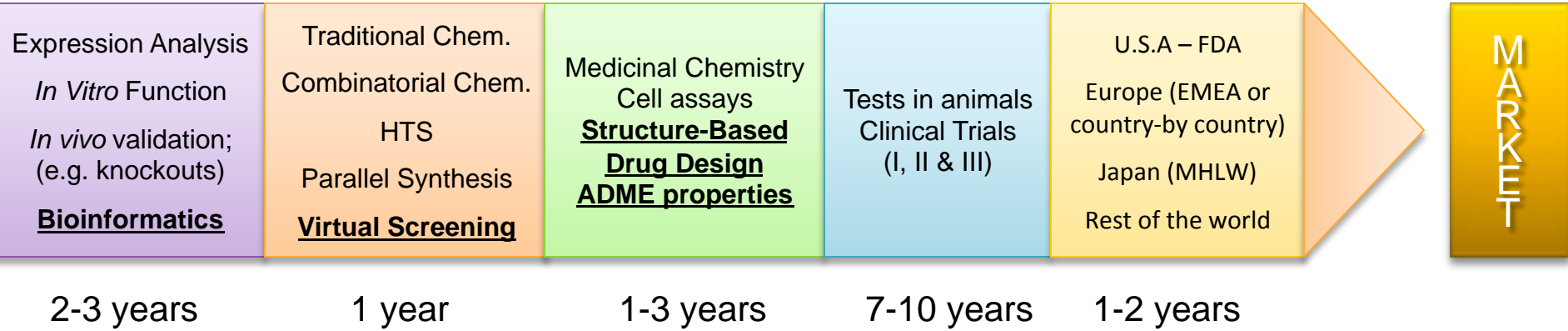
Total cost ≈ 1.000 -2.000 million € (630 billion pesos – 1.3 trillion pesos)

Drug Discovery – an Introduction



Drug Discovery and Development Pipeline

Target Discovery Lead Discovery Lead Opt. Pre-D&Develop. Registration



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The role of patents

Drug Discovery – an Introduction



Drug Discovery and Development Pipeline

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Fields where computational
 biochem can contribute

Fields where computational
 biochem does not contribute

Drug Discovery – an Introduction



Pharmacokinetics & Pharmacodynamics

Drug Discovery – an Introduction



Pharmacokinetics & Pharmacodynamics

Pharmacokinetics



What the body does to the drug

Drug Discovery – an Introduction



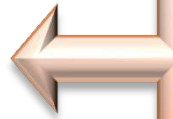
Pharmacokinetics & Pharmacodynamics

Pharmacokinetics



What the body does to the drug

Pharmacodynamics



What the drug does to the body

Drug Discovery – an Introduction



Pharmacokinetics

Absortion

Drug Discovery – an Introduction



Pharmacokinetics

Absorption



Physical properties that promote absorption

Drug Discovery – an Introduction



Pharmacokinetics

Absorption

Physical properties that promote absorption



Distribution

Drug Discovery – an Introduction



Pharmacokinetics

Absorption

Physical properties that promote absorption



Distribution

Physical properties that promote distribution



Drug Discovery – an Introduction



Pharmacokinetics

Absorption

Physical properties that promote absorption

Distribution

Physical properties that promote distribution

Metabolism

Drug Discovery – an Introduction



Pharmacokinetics

Absorption

Physical properties that promote absorption

Distribution

Physical properties that promote distribution

Metabolism

Binding to specific metabolic enzymes,
Chemical groups that are metabolic targets

Drug Discovery – an Introduction



Pharmacokinetics

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Physical properties that promote distribution

Metabolism

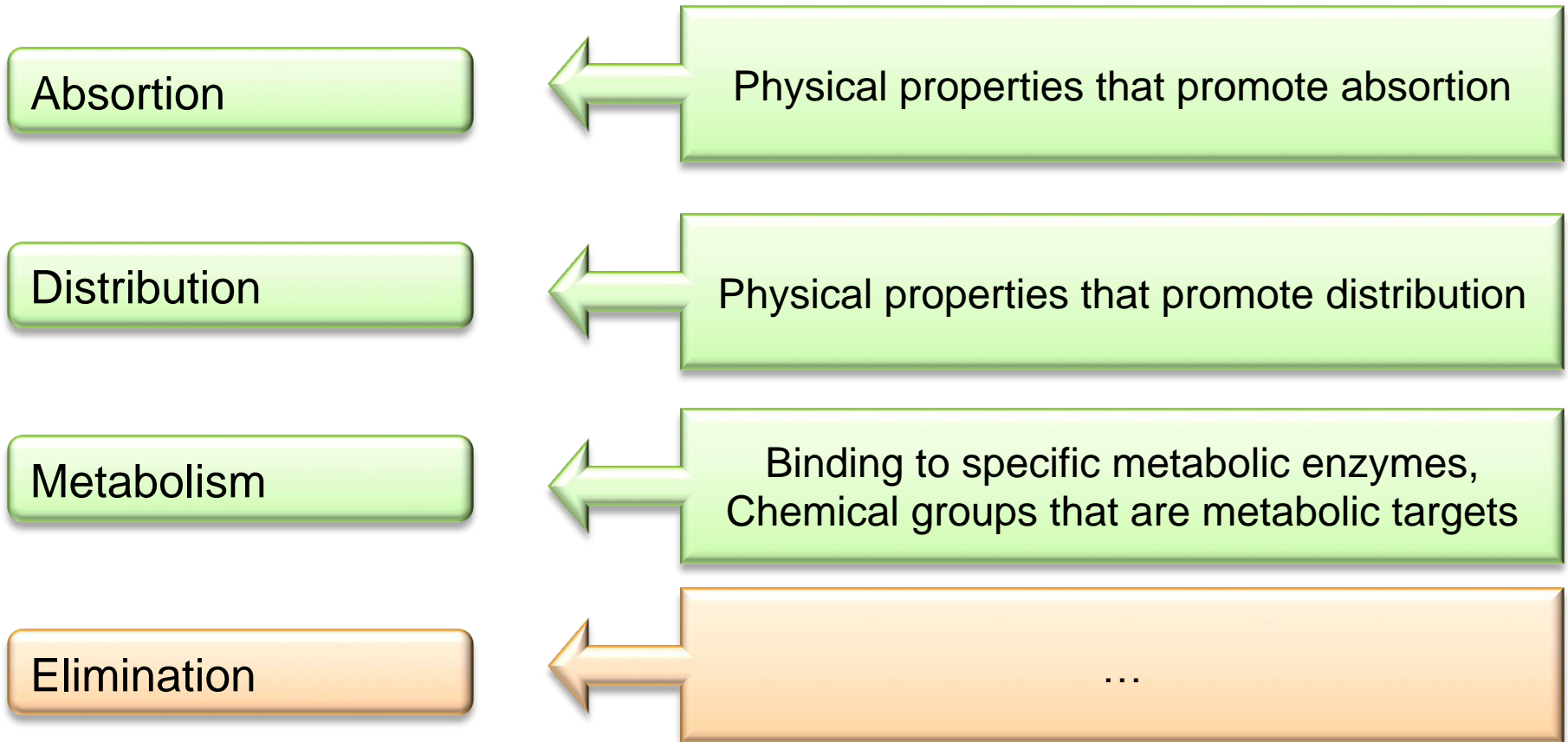
Binding to specific metabolic enzymes,
Chemical groups that are metabolic targets

Elimination

Drug Discovery – an Introduction



Pharmacokinetics



Drug Discovery – an Introduction



Can we predict toxicity?

Drug Discovery – an Introduction



Can we predict toxicity?

Databases tell us if the compound is listed as toxic

Drug Discovery – an Introduction



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Databases tell us if the compound has moieties listed as toxic

Drug Discovery – an Introduction



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Databases tell us if the moieties are metabolic and hydrolytic stable

Drug Discovery – an Introduction



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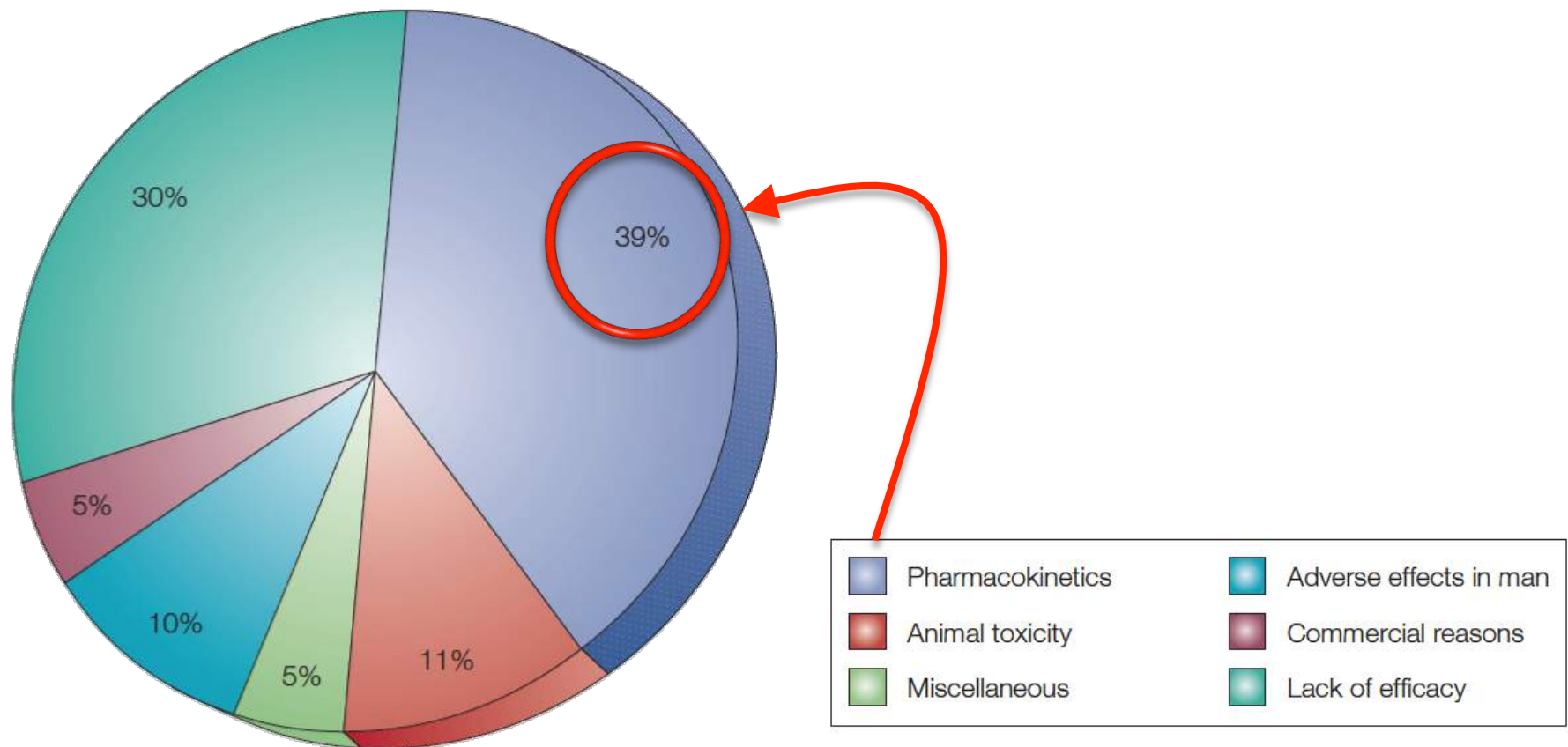
Databases tell us if the moieties are metabolic and hydrolytic stable

BUT...

Drug Discovery – an Introduction



Causes of Failure in Drug Discovery & Development



Drug Discovery – an Introduction



The role of the Computational Biochemist

Drug Discovery – an Introduction



The role of the Computational Biochemist

Help to select the initial compounds to be synthesized



The role of the Computational Biochemist

Help to select the initial compounds to be synthesized

Help to increase the affinity of a given compound



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Help to increase the affinity of a given compound

Predict the chances of a compound to be bioavailable



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Predict failure

Drug Discovery – an Introduction



The role of the Computational Biochemist

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Predict failure

Avoid animal tests

Drug Discovery – an Introduction



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