

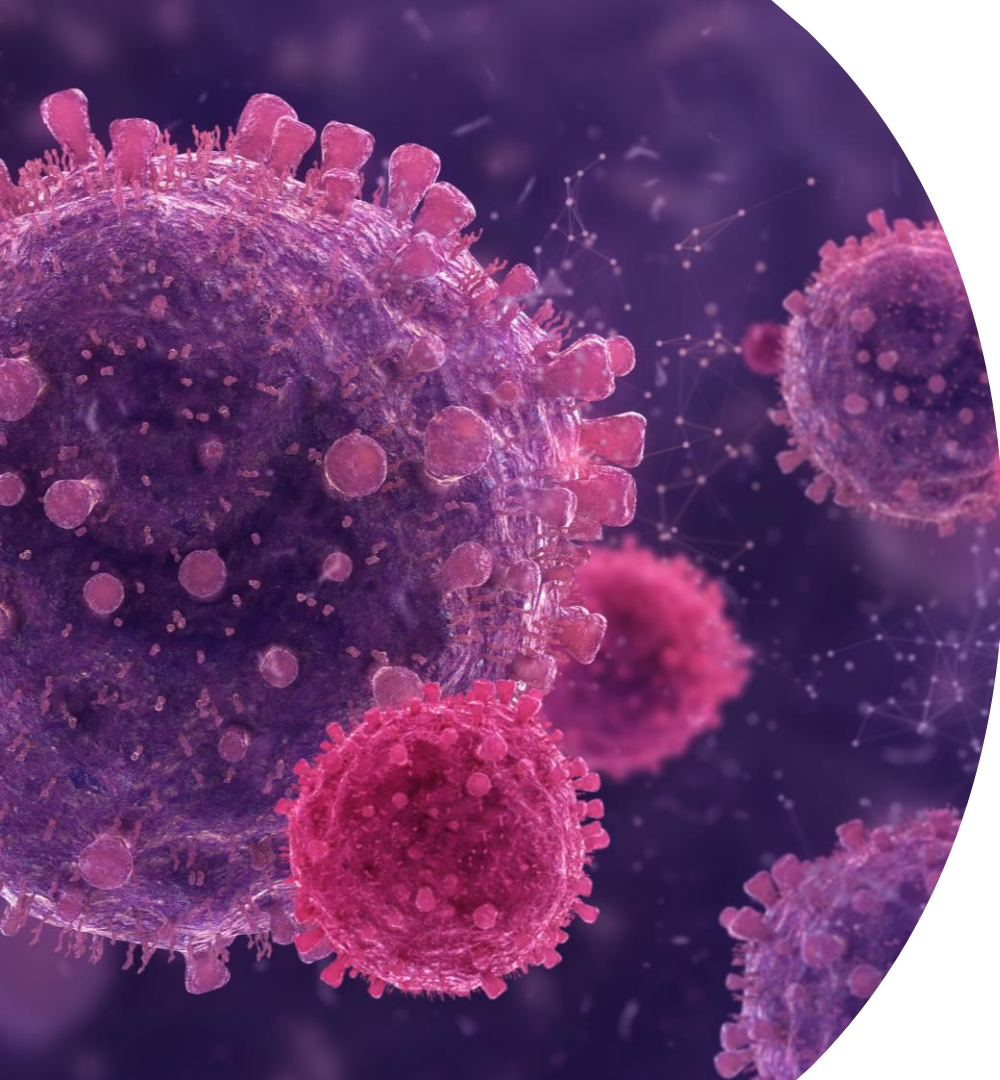


**Grasping opportunities for
better drug discovery:
Interdisciplinarity, deeper insights
into disease, new technologies
and better decision-making**

Karl-Heinz Baringhaus

Sanofi

Site Director R&D Frankfurt



sanofi

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Grasping the opportunities
for better drug discovery:
interdisciplinarity, deeper
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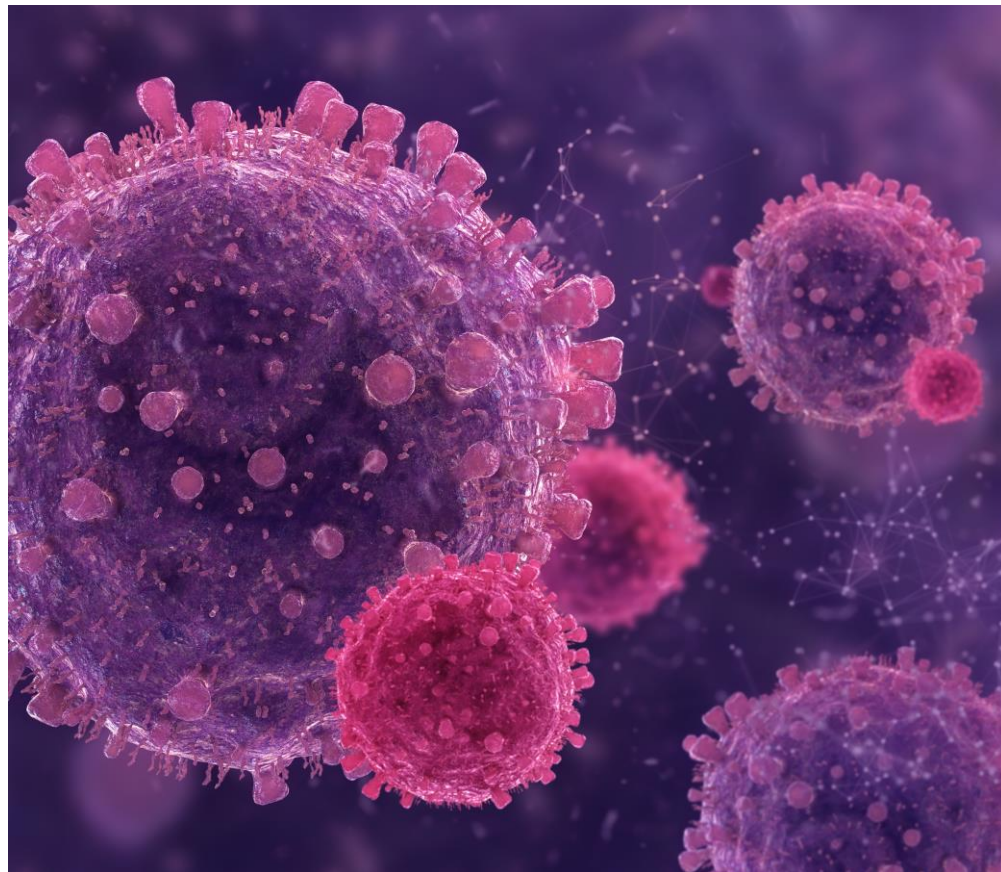
ChemTalks

September 2024

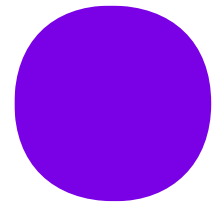
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Karl-Heinz Baringhaus

Topics

- 1 Introduction
- 2 Understanding Disease
- 3 New Technologies
- 4 AI in Drug Discovery
- 5 Better Decision Making
- 6 Summary & Conclusion



1 Introduction



Introduction

- **1990:** Combinatorial Chemistry revolutionizes Drug Discovery
- **1998:** Chemoinformatics: A New Era in Drug Discovery
- **2001:** Mapping of the Human Genome: Health benefits could be phenomenal
- **2017:** Artificial Intelligence: Better drugs faster

The long road to a new drug



Focus on disease



Target identification



Screening



Development of active ingredient candidate



Pre-clinical development



Clinical phase I



Clinical phase II



Clinical phase III



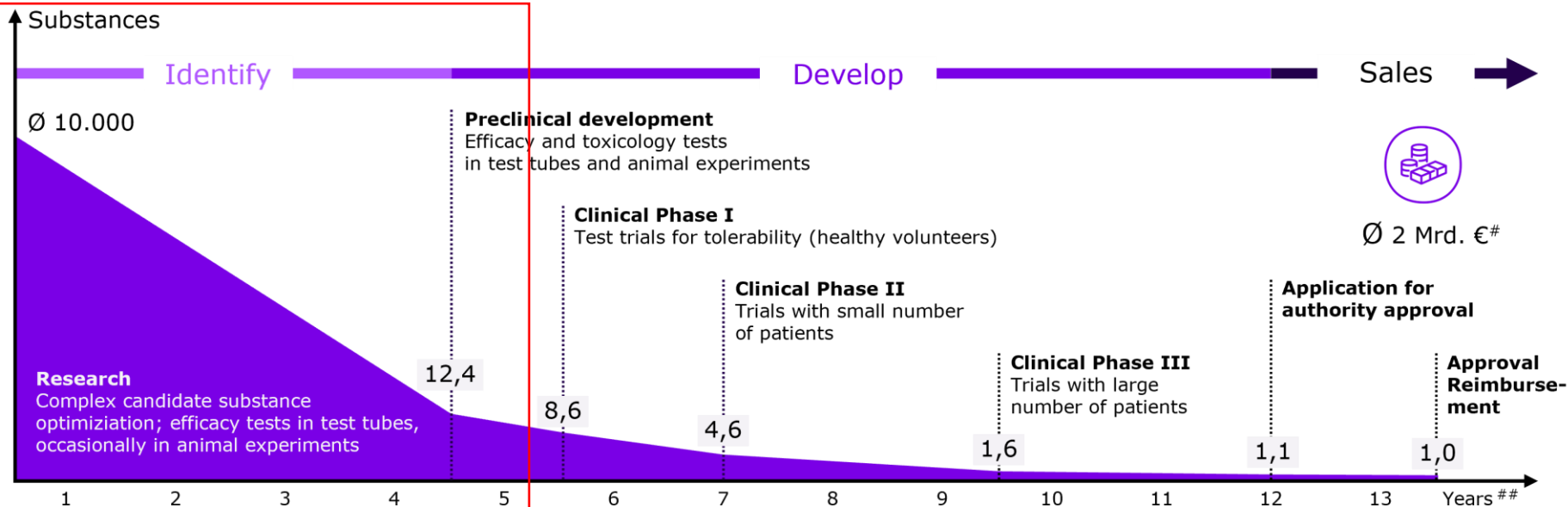
Approval



Prescription, monitoring



Sales



The long road to a new drug

Complexity



Low Probability of Success

At each drug discovery phase presents challenges and uncertainty regarding efficacy, safety, market competition and regulatory hurdles



Long Cycle Time

To bring a new drug to market can take over 5+ years because it requires extensive research, iterative preclinical testing, clinical trials and regulatory approval.



Costly Investment

Drug discovery requires heavy financial investment which is attributed to expensive experiments, technology, clinical trials, regulatory compliance, and skilled personnel.



High Complexity & Uncertainty

With the limited depth of information and high uncertainty, when identifying leads, targets, sample analysis and patient selections makes determining the best action highly complex for scientist

The numbers speak For themselves



Cost per successful launch is increasing by ~50% annually

Despite improved success rates, cost per successful launch reached \$2.6B in 2016



60% of R&D costs are driven by clinical failures

Out of 2.6 Bn USD development costs (accounted for failed assets), 1.5 Bn attributed to failed trials

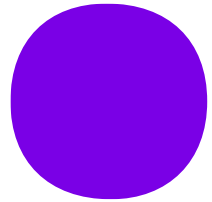


Only top 20% of companies realize a break even...

...on their R&D investments after 7 years

2

Understanding Disease



Understanding Disease



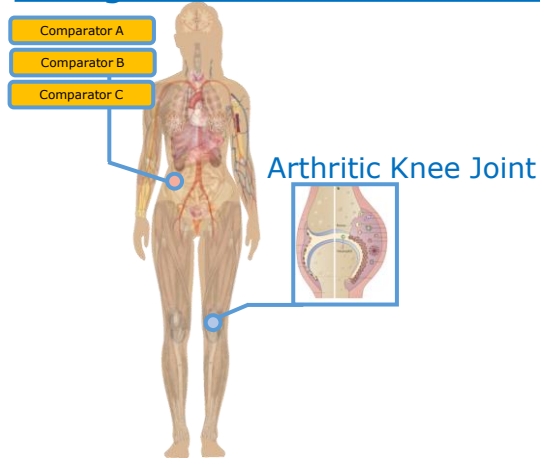
Understanding human diseases is a complex and multifaceted challenge

- 1. Complexity of Biological Systems:** The human body is incredibly complex, with numerous interacting systems and processes: multiple genes, proteins and pathways
- 2. Genetic Variability:** Each person's genetic makeup is unique, diseases can manifest differently in different individuals: universal treatments?
- 3. Environmental Factors:** Lifestyle, diet, exposure to toxins, and other environmental factors: high variability between individuals and populations
- 4. Data Integration:** Modern research generates vast amounts of data including genomics, proteomics, and clinical records: data integration, making sense of data, drawing meaningful conclusions is a challenge

Example: Translational Disease Modeling for Rheumatoid Arthritis

Building a computer model of disease

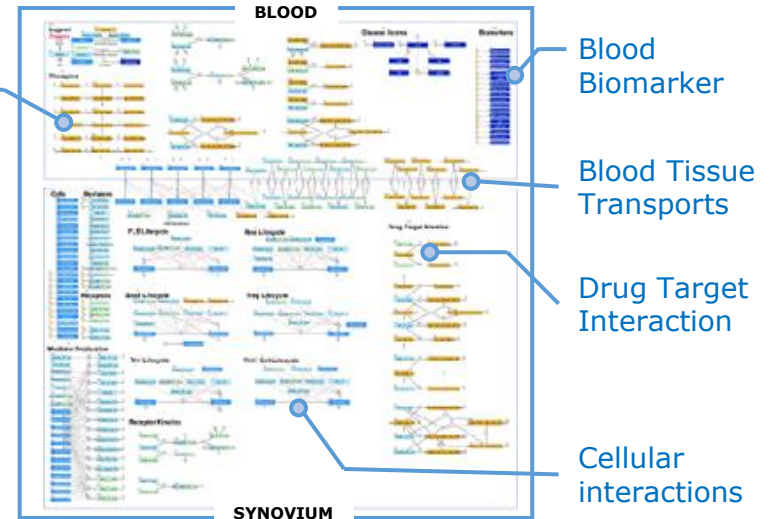
Biological View on Sites of Inflammation:



Nanobodies
Pharmacokinetics



Computer Model of Inflammation:



Input from various partners & KOLs

Model building focusses on relevant tissues, key interactions and include the latest, most informative data: synovium & blood

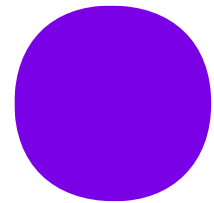
Understanding Disease

1. Do we understand the disease?
2. Do we have a complete overview of disease related targets and how they influence the disease?
3. Was target validation accomplished? Do we have valid biomarkers?
4. Do proper and validated cellular and animal models exist for preclinical testing?
5. What modalities should preferentially be used for treatment?
6. Is a data strategy available to deal with vast amounts of data from genomics, proteomics, and later clinical records including meaningful decision generation and validation?



3

New Technologies



New Technologies

- **Artificial Intelligence (AI) and Machine Learning (ML)**

AI and ML are revolutionizing drug discovery by automating data processing



- **Gene editing**

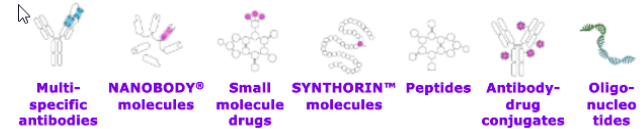
CRISPR-Cas9 gene editing technology open the door for gene therapy

- **Advanced Assay Development**

New assay technologies for cost-effective and successful drug research

- **Synthetic Biology**

Access to new type of modalities



- **High-Performance Computing for analyzing large datasets**

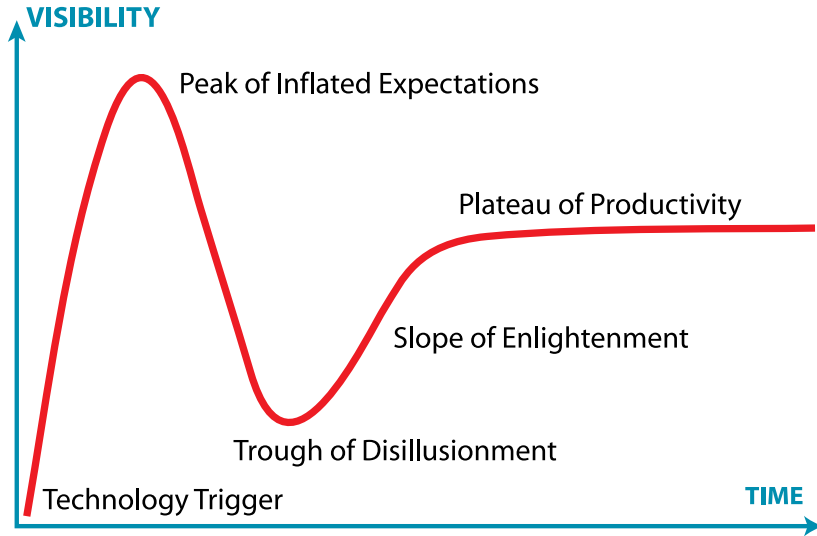


- **3D Cell Cultures**

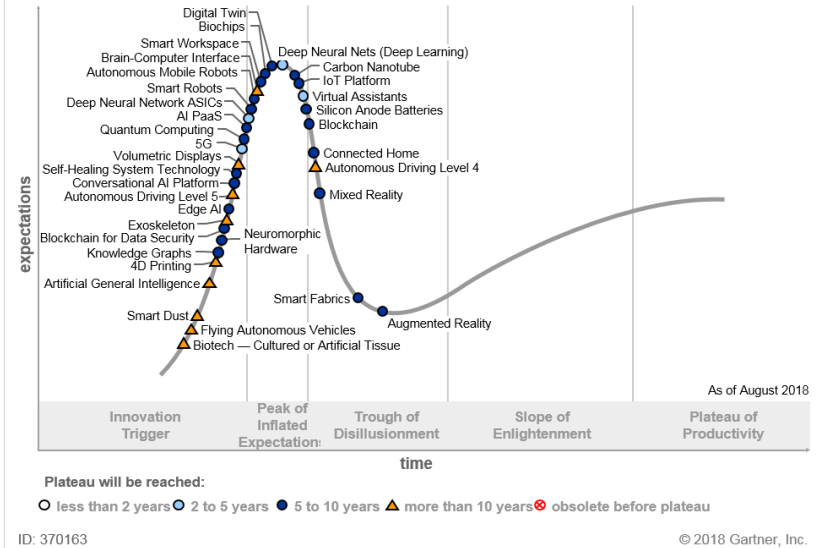
Growing cells in a three-dimensional environment



New Technologies Gartner hype cycle

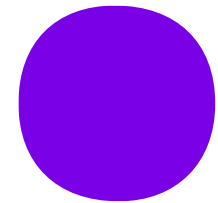


Hype Cycle for Emerging Technologies, 2018



4

Artificial Intelligence in Drug Discovery



Artificial Intelligence in Drug Discovery

NEWS

Home Video World UK Business Tech Science Stories Entertainment & Arts

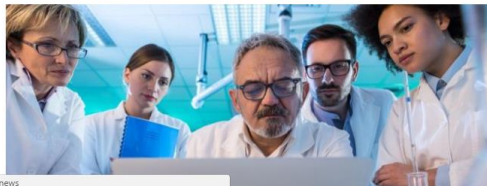
Business Market Data Markets Global Trade Companies Entrepreneurship | Tech

Better drugs, faster: The potential of AI-powered humans

By Emma Woolcott
Technology of Business reporter

1 August 2017

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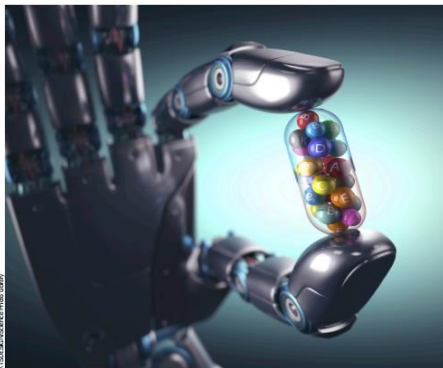
tv/news

NEWS

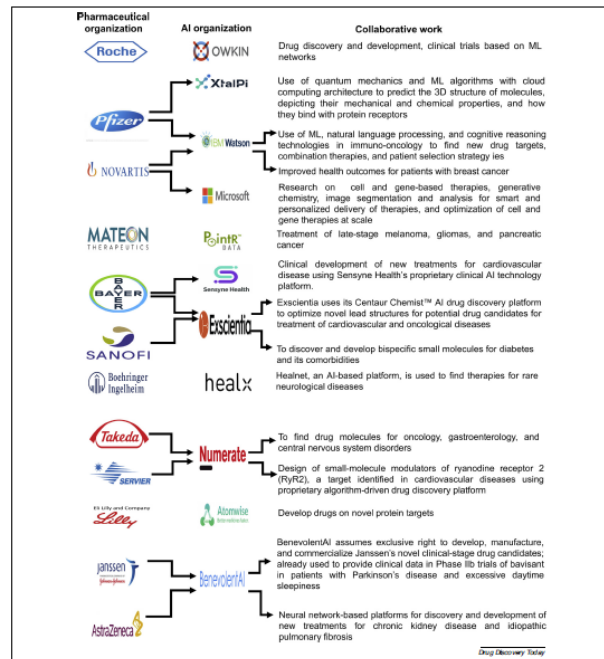
AI-powered drug discovery captures pharma interest

A drug-hunting deal inked last month, between Numerate, of San Bruno, California, and Takeda Pharmaceutical to use Numerate's artificial intelligence (AI) suite to discover small-molecule therapies for oncology, gastroenterology and central nervous system disorders, is the latest in a growing number of research alliances involving AI-powered computational drug development firms. Also last month, GNS Healthcare of Cambridge, Massachusetts announced a deal with Roche subsidiary Genentech of South San Francisco, California to use GNS's AI platform to better understand what affects the efficacy of known therapies in oncology. In May, Exscientia of Dundee, Scotland, signed a deal with Paris-based Sanofi that includes up to €250 (\$280) million in milestone payments. Exscientia will provide the compound design and Sanofi the chemical synthesis of new drugs for diabetes and cardiovascular disease. The trend indicates that the pharma industry's long-running skepticism about AI is softening into genuine interest, driven by AI's promise to address the industry's principal pain point: clinical failure rates.

The industry's willingness to consider AI approaches reflects the reality that drug discovery is laborious, time consuming and not particularly effective. A two-decade-long downward



Ref.: Nature Biotechnology, 2017, 35, 604-605.



Ref.: Drug Discovery Today, 2021, 26, 80-93.

Active research within many Biotech companies

- Examples are

Numerate

BenevolentAI

Exscientia
DRIVEN BY KNOWLEDGE

twoAR

sanofi

AI in Compound Discovery

Target ID

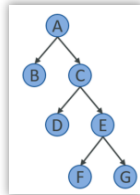
Lead ID

Lead optimization

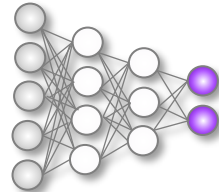
Preclinical candidate



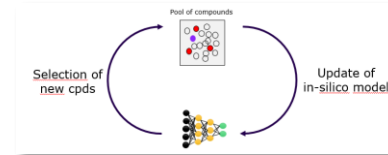
AlphaFold



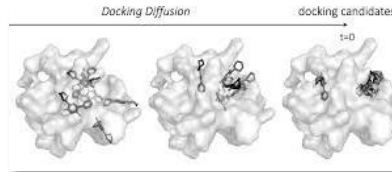
Synthesis Prediction



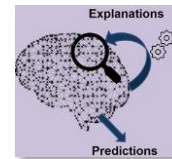
AI/ML for Property Prediction



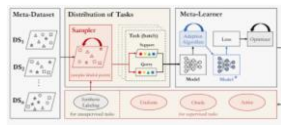
Active Learning



Diffusion models

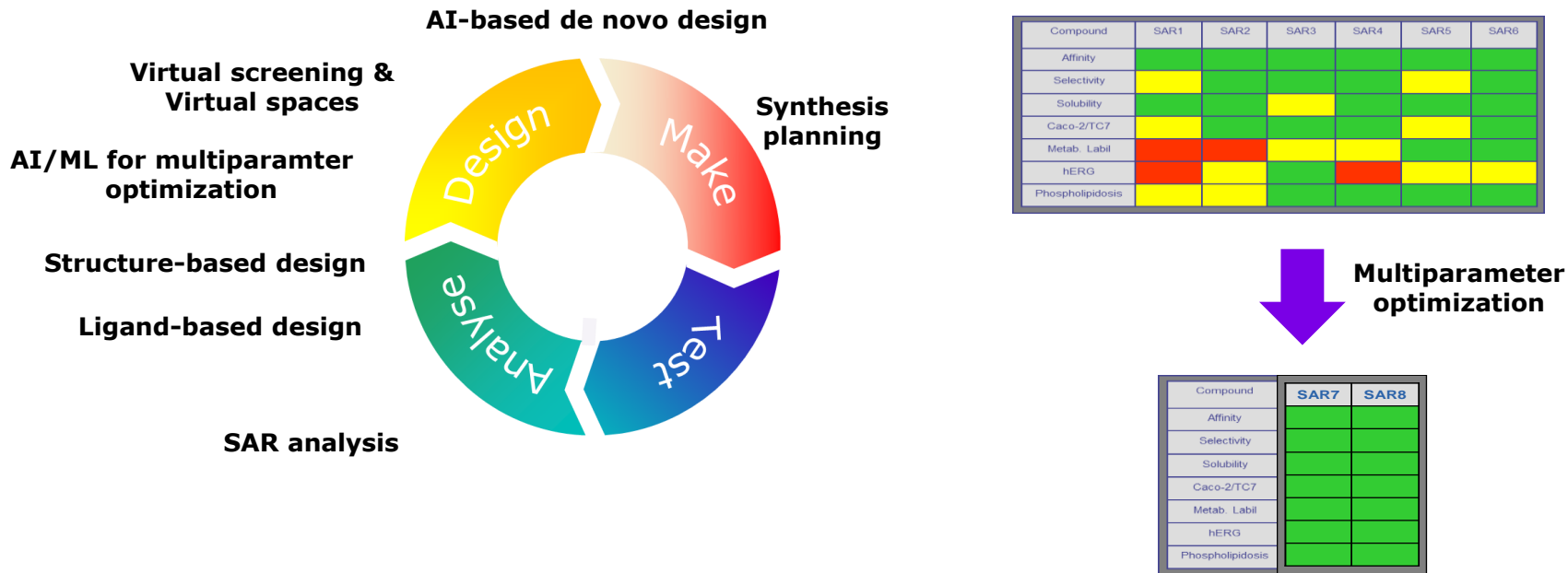


SAR analysis – Explainable AI



Generative AI

Navigate Drug Discovery: Design-Make-Test-Analyse



AI accelerates DMTA cycle by

- Turning data into knowledge for a desired property profile
- Exploiting *in-silico* approaches for the design of novel compounds

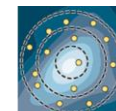
AI Drives Design of Novel Compounds

Virtual DMTA cycles drive design of novel compounds

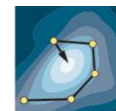
- In-silico search through chemical space for optimal compound profiles
- Two key components: Compound generation & property prediction



Property prediction

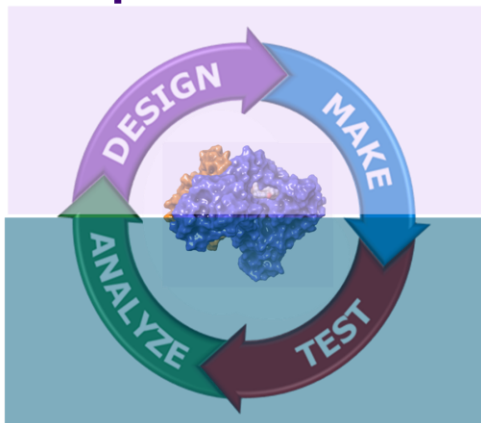


Virtual Chemical Spaces



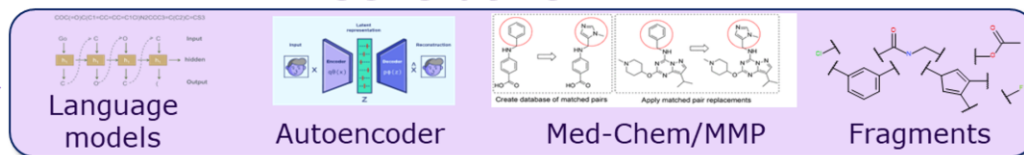
De novo design

Compound Generation

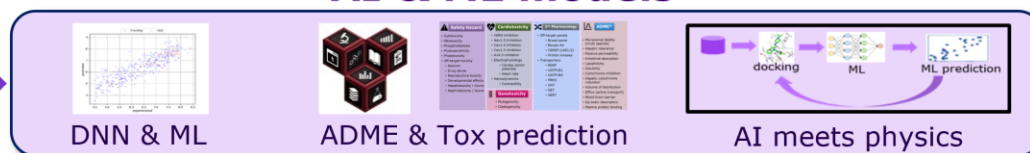


Property prediction

Generative AI



AI & ML models



Self-driving labs (SDLabs)

Revolutionizing Research: How AI-Driven Chemistry Labs Are Redefining Discovery

TOPICS: Artificial Intelligence Biochemistry North Carolina State University Pharmaceuticals

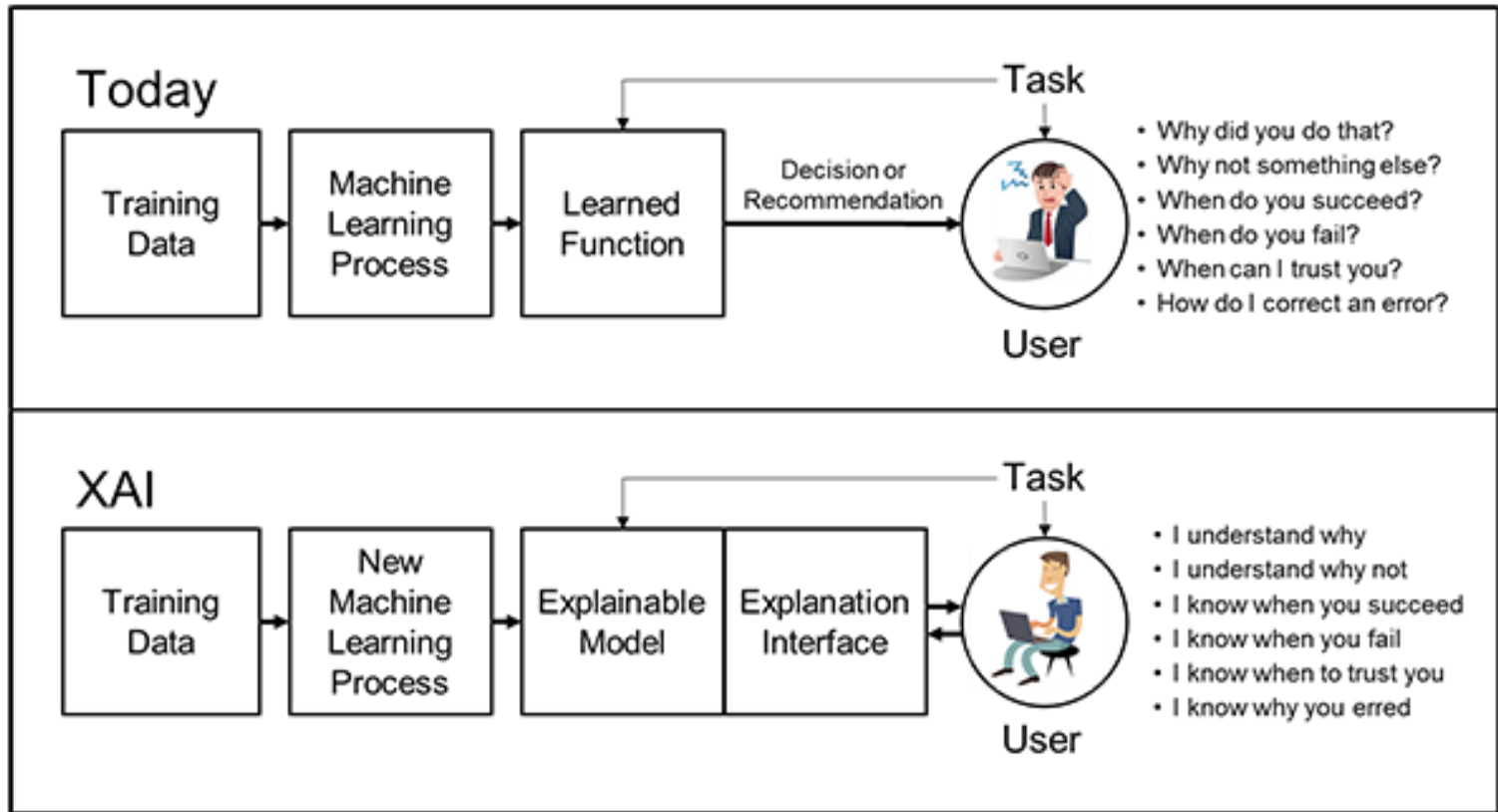
By NORTH CAROLINA STATE UNIVERSITY FEBRUARY 16, 2024



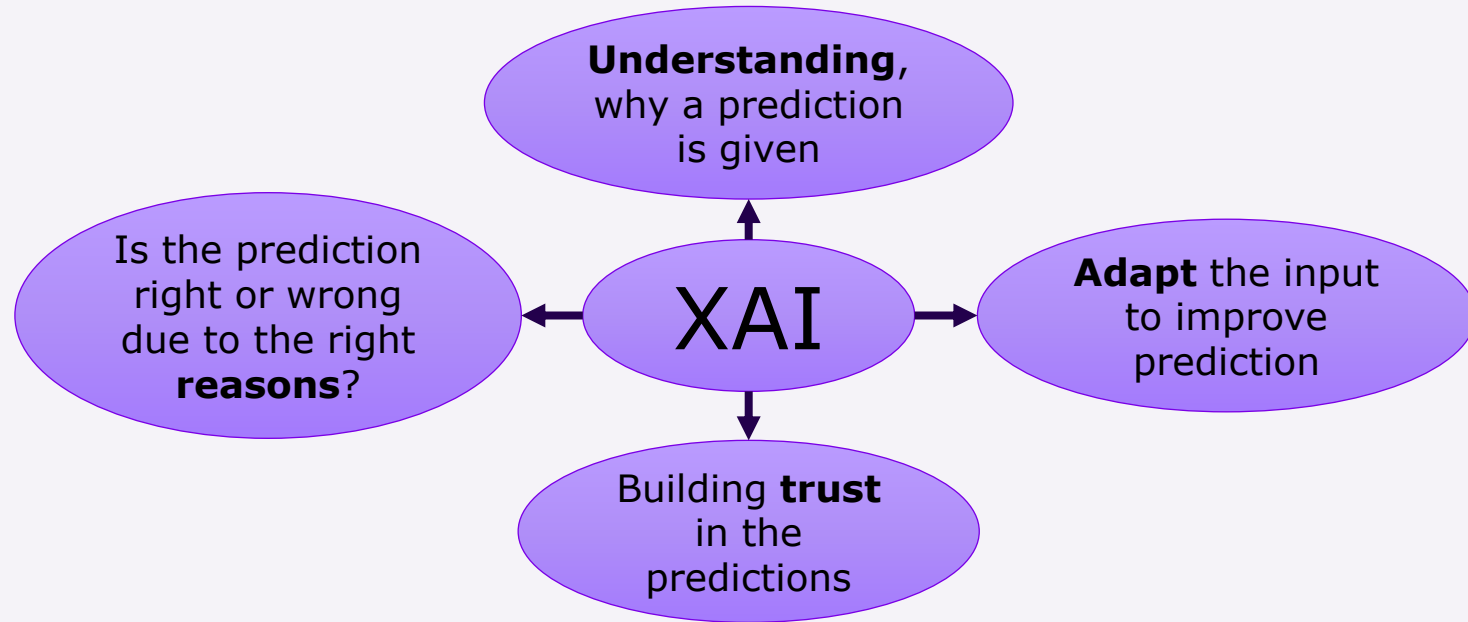
The advancement of self-driving labs in chemistry and materials science, employing AI and automation, promises to revolutionize research by accelerating the discovery of new molecules and materials. Milad Abolhasani highlights the need for standardized definitions and performance metrics to compare and improve these technologies effectively. Credit: SciTechDaily.com

- 1. Accelerated Research and Development**
- 2. High-Throughput Experimentation**
- 3. Reduced Human Error**
- 4. Data Generation and Analysis**
- 5. Resource Efficiency**
- 6. Transition to a Circular Economy**

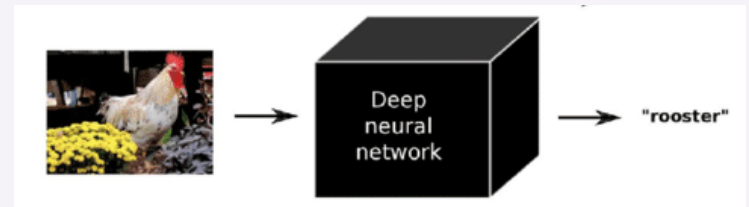
Can we also explain the predictions?



Explainable AI: why do we need it?

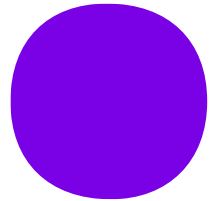


Remove blackbox-character of neural network predictions



5

Better Decision Making



Better Decision Making

- **Utilize Advanced Data Analytics:**
Leveraging AI and machine learning
- **Incorporate Model-Informed Drug Discovery and Development (MID3)**
Integration of data from various sources to create comprehensive models that predict drug behavior and efficacy
- **Mitigate Bias**
Recognizing and addressing biases in decision-making
- **Enhance Collaboration**
Collaborative research and open data sharing among pharmaceutical companies, academic institutions, and regulatory bodies
- **Continuous Learning and Adaptation**
Dynamic drug discovery processes with continuous learning from past successes and failures

Example: Large Pool of *In-Silico* ADMET Models

In-silico Models for Targets, ADME and Safety Properties

Physicochem. properties

- Aqueous solubility
- logP, logD, pKa

Permeability

- Caco-2 permeability
- Efflux
- Plasma protein binding
- Blood-brain barrier
- Transporter interaction

Metabolism / Drug-drug int.

- Microsomal lability & clearance
- HES clearance
- CYP450-inhibition (CYP3A4, 2D6, 2C9)
- Site-of-metabolism
- Volume of distribution
- Halflife $t_{1/2}$
- Intrinsic clearance
- Mechanism-b. inh.
- PXR agonism
- CYP3A4 induction

Safety

- hERG channel
- Nav1.5 and others
- Cav1.2 and others
- Phospholipidosis
- Genotoxicity (MNT)
- Organ toxicity
- Phototoxicity

Off-targets

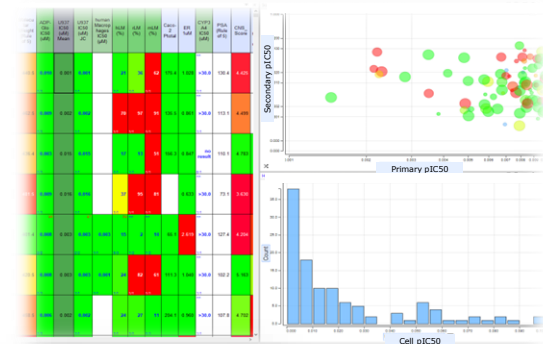
- Target-prediction panel for receptor, ion channel and kinase profiles.

Close collaboration between chemistry, pharmacokinetics, preclinical safety

Model collection supports **multidimensional optimization**.

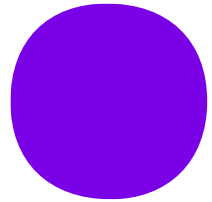
Constant updates cover emerging **chemical space**.

Available to scientists via **Predict360**, **StarDrop** and **LiveDesign**.



6

Summary & Conclusion



Summary & Conclusion

- **Close collaboration across biology, chemistry and data science is mandatory**
- **Advances in genomics, proteomics and other omics technologies foster deep understanding of diseases**
- **Artificial Intelligence and high-throughput technologies speed up drug discovery**
- **Data analytics and decision-making tools are compulsory to make informed decisions**



...and last but not least



The most popular individuum from Frankfurt
Johann-Wolfgang von Goethe (1749 -1832)

Es ist nicht genug, zu wissen, man muß auch anwenden;
es ist nicht genug, zu wollen, man muß auch tun.

It's not enough to know, you also have to apply
It's not enough to want, you also have to do

Il ne suffit pas de savoir, encore faut-il appliquer
Vouloir n'est pas suffisant, il faut aussi faire



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Thank you
•

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