AI-BASED DRUG DEVELOPMENT AND REPURPOSING THERAPIES

Chances and challenges for breast cancer

Prof. Evelyne Bischof, MD, MPH, FEFIM

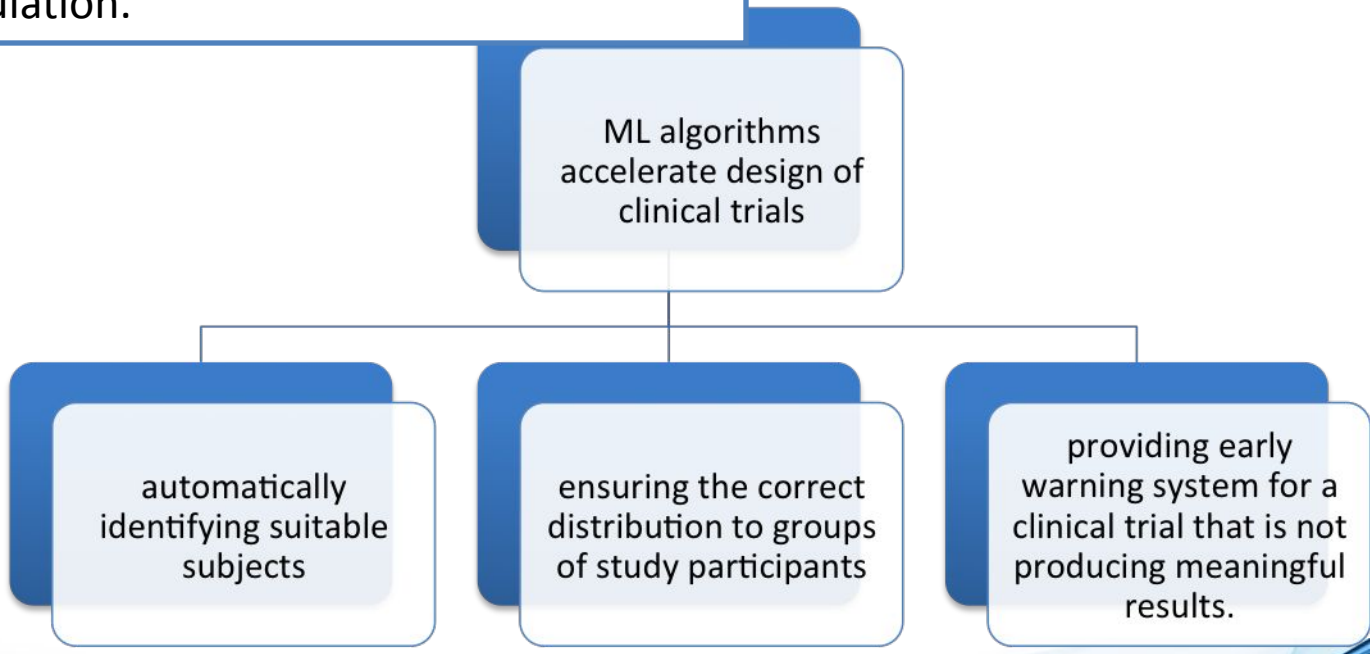
Personalized therapies

AI-based drug development is an integral element!

AI can be harnessed towards pharmacostrategies in various steps

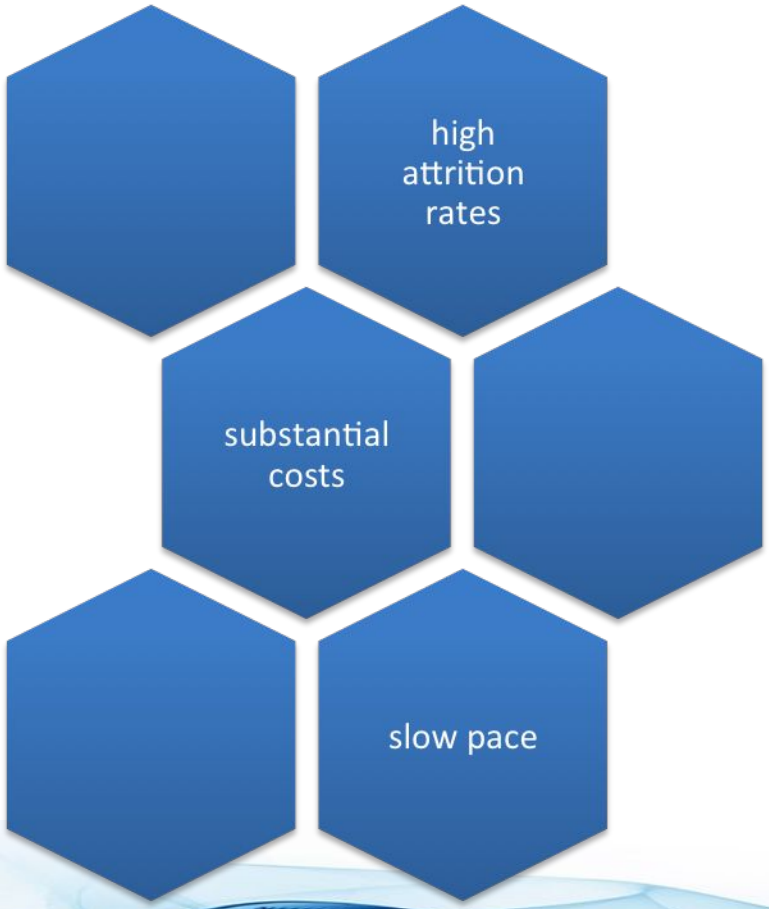
Personalized therapies

If a drug has been proposed as a potential treatment approach based on empirical clinical observation, AI could and should be capitalized to rapidly simulate efficacy and side effects in (preferably stratified) population.



Status quo

The drug discovery process today



Drug discovery is one of the most complex, risky, and lengthy areas of human development. This process takes decades, billions of dollars, and fails over 90% of the time.

There are very few truly novel drugs on the market. In 2020, the FDA approved 53 novel drugs, and that was the record year.

Many of these drugs were small molecules that modulated the function of well-known molecular targets. Discovering a novel molecule for a novel target for a broad disease indication is extremely rare.

Status quo

The drug discovery process today

Regulatory bodies introduced new programs, allowing the review and authorization of these treatments to be fast-tracked.

accelerate the R&D for various targets

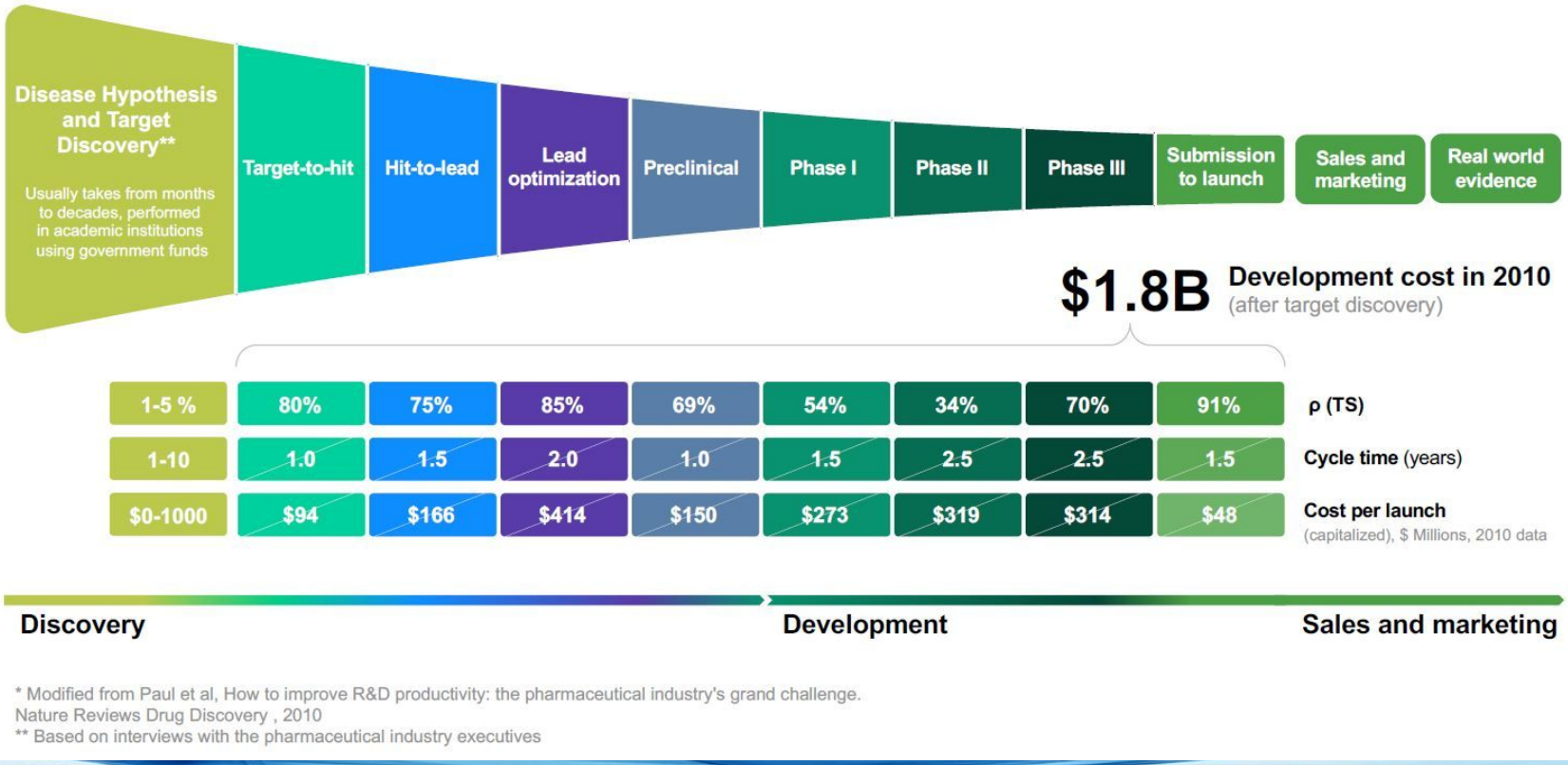
Status quo

The drug discovery process today and yesterday

Traditional drug R&D takes >10 years and >$2.6B

for a novel drug from discovery to launch (in 2010 and constantly increasing)

Insilico Medicine

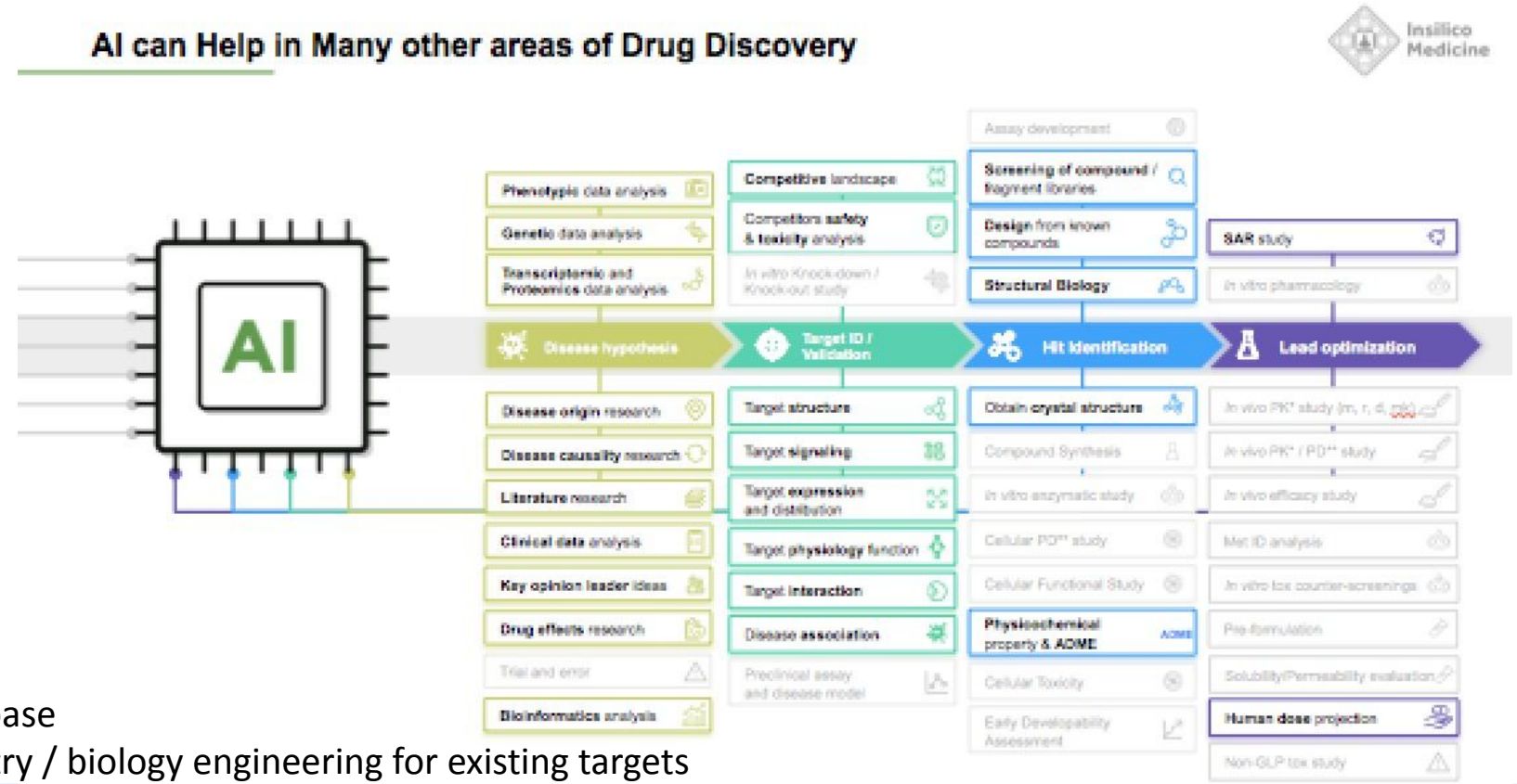


* Modified from Paul et al, How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nature Reviews Drug Discovery , 2010

** Based on interviews with the pharmaceutical industry executives

Drug discovery

The drug discovery process today



- Target-base
- Chemistry / biology engineering for existing targets
- Development of personalized medicine solutions

Drug discovery

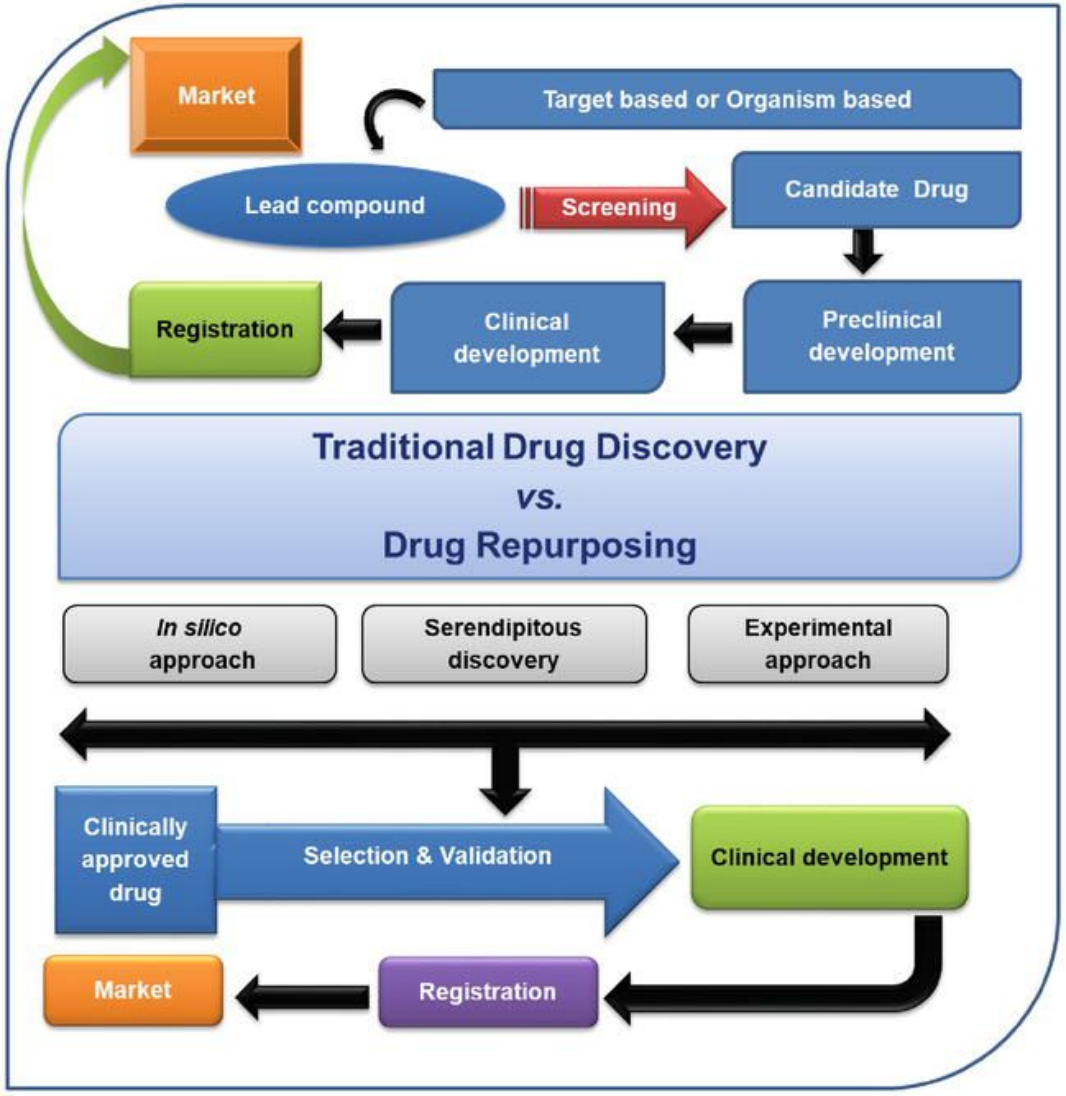
Large amounts of data coming from robotics experiments or clinical data, or a combination used.

Some targets already entered human clinical trials (by in-licensing compounds).

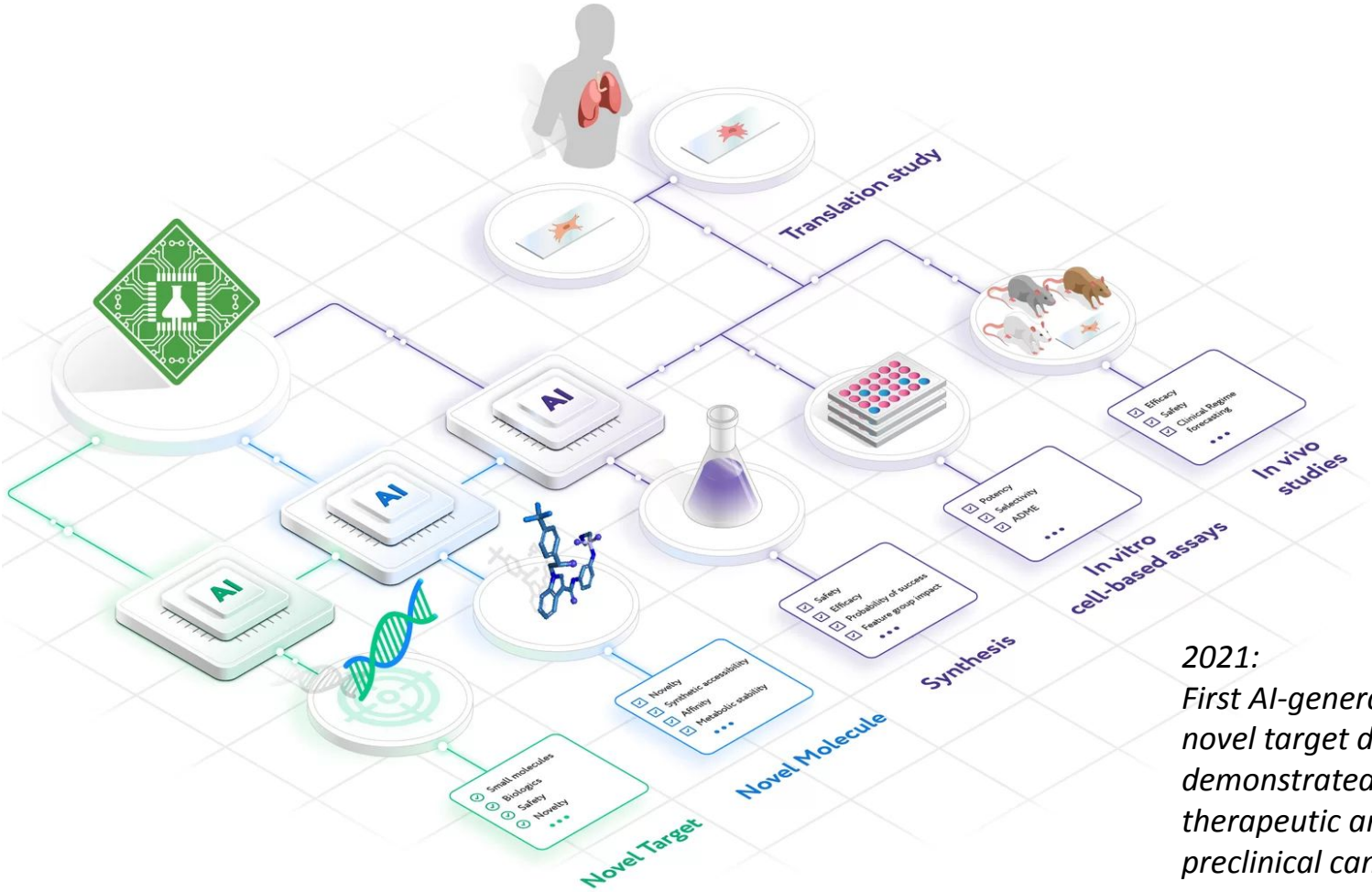
But…

Can AI identify

Novel Targets and **Novel Molecules?**



Drug discovery



2021:
First AI-generated novel molecule for a novel target discovered with AI demonstrated efficacy in a broad therapeutic area and reached preclinical candidate stage.

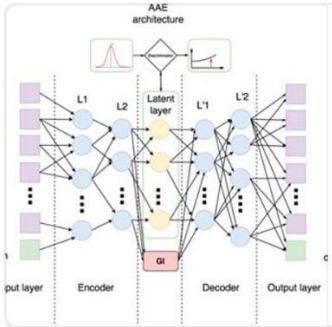
Drug discovery

Yann LeCun liked this.

Yoshua Bengio

2 hrs ·

Auto-encoders with a GAN objective in the latent layer for cancer drug discovery:



Oncotarget | The cornucopia of meaningful leads: Applying...

doi:10.18632/oncotarget.14073. Artu...

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Yann LeCun and 340 others 64 Shares

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January 2017

Drug discovery

nature biotechnology

BRIEF COMMUNICATION

https://doi.org/10.1038/s41587-019-0224-x

Deep learning enables rapid identification of potent DDR1 kinase inhibitors

Alex Zhavoronkov[1*], Yan A. Ivanenkov[1], Alex Aliper[1], Mark S. Veselov[1], Vladimir A. Aladinskiy[1], Anastasiya V. Aladinskaya[1], Victor A. Terentiev[1], Daniil A. Polykovskiy[1], Maksim D. Kuznetsov[1], Arip Asadulaev[1], Yury Volkov[1], Artem Zholus[1], Rim R. Shayakhmetov[1], Alexander Zhebrak[1], Lidiya I. Minaeva[1], Bogdan A. Zagribelnyy[1], Lennart H. Lee[2], Richard Soll[2], David Madge[2], Li Xing[2], Tao Guo[2] and Alán Aspuru-Guzik[3,4,5,6]

We have developed a deep generative model, generative tensorial reinforcement learning (GENTRL), for de novo small-molecule design. GENTRL optimizes synthetic feasibility, novelty, and biological activity. We used GENTRL to discover potent inhibitors of discoidin domain receptor 1 (DDR1), a kinase target implicated in fibrosis and other diseases, in 21 days. Four compounds were active in biochemical assays, and two were validated in cell-based assays. One lead candidate was tested and demonstrated favorable pharmacokinetics in mice.

Drug discovery is resource intensive, and involves typical timelines of 10–20 years and costs that range from US$0.5 billion to US$2.6 billion[1,2]. Artificial intelligence promises to accelerate this process and reduce costs by facilitating the rapid identification of compounds[3,4]. Deep generative models are machine learning techniques that use neural networks to produce new data objects. These techniques can generate objects with certain properties, such as activity against a given target, that make them well suited for the discovery of drug candidates. However, few examples of generative drug design have achieved experimental validation involving synthesis of novel compounds for in vitro and in vivo investigation[5–16].

Discoidin domain receptor 1 (DDR1) is a collagen-activated pro-inflammatory receptor tyrosine kinase that is expressed in epithelial cells and involved in fibrosis[17]. However, it is not clear whether DDR1 directly regulates fibrotic processes, such as myofibroblast activation and collagen deposition, or earlier inflammatory events that are associated with reduced macrophage infiltration. Since 2013, at least eight chemotypes have been published as selective DDR1 (or DDR1 and DDR2) small-molecule inhibitors (Supplementary Table 1). Recently, a series of highly selective, spiro-indoline-based DDR1 inhibitors were shown to have potential therapeutic efficacy against renal fibrosis in a *Col4a3*$^{-/-}$ mice model of Alport syndrome[18]. A wider diversity of DDR1 inhibitors would therefore enable further basic understanding and therapeutic intervention.

We developed generative tensorial reinforcement learning (GENTRL), a machine learning approach for de novo drug design. GENTRL prioritizes the synthetic feasibility of a compound, its effectiveness against a given biological target, and how distinct it is from other molecules in the literature and patent space. In this work, GENTRL was used to rapidly design novel compounds that are active against DDR1 kinase. Six of these compounds, each complying with Lipinski's rules[1], were designed, synthesized, and experimentally tested in 46 days, which demonstrates the potential of this approach to provide rapid and effective molecular design (Fig. 1a).

To create GENTRL, we combined reinforcement learning, variational inference, and tensor decompositions into a generative two-step machine learning algorithm (Supplementary Fig. 1)[19]. First, we learned a mapping of chemical space, a set of discrete molecular graphs, to a continuous space of 50 dimensions. We parameterized the structure of the learned manifold in the tensor train format to use partially known properties. Our auto-encoder-based model compresses the space of structures onto a distribution that parameterizes the latent space in a high-dimensional lattice with an exponentially large number of multidimensional Gaussians in its nodes. This parameterization ties latent codes and properties, and works with missing values without their explicit input. In the second step, we explored this space with reinforcement learning to discover new compounds.

GENTRL uses three distinct self-organizing maps (SOMs) as reward functions: the trending SOM, the general kinase SOM, and the specific kinase SOM. The trending SOM is a Kohonen-based reward function that scores compound novelty using the application priority date of structures that have been disclosed in patents. Neurons that are abundantly populated with novel chemical entities reward the generative model. The general kinase SOM is a Kohonen map that distinguishes kinase inhibitors from other classes of molecules. The specific kinase SOM isolates DDR1 inhibitors from the total pool of kinase-targeted molecules. GENTRL prioritizes the structures it generates by using these three SOMs in sequence.

We used six data sets to build the model: (1) a large set of molecules derived from a ZINC data set, (2) known DDR1 kinase inhibitors, (3) common kinase inhibitors (positive set), (4) molecules that act on non-kinase targets (negative set), (5) patent data for biologically active molecules that have been claimed by pharmaceutical companies, and (6) three-dimensional (3D) structures for DDR1 inhibitors (Supplementary Table 1). Data sets were preprocessed to exclude gross outliers and to reduce the number of compounds that contained similar structures (see Methods).

We started to train GENTRL (pretraining) on a filtered ZINC database (data set 1, described earlier), and then continued training using the DDR1 and common kinase inhibitors (data set 2 and data set 3). We then launched the reinforcement learning stage with the reward described earlier. We obtained an initial output of 30,000 structures (Supplementary Data Set), which were then

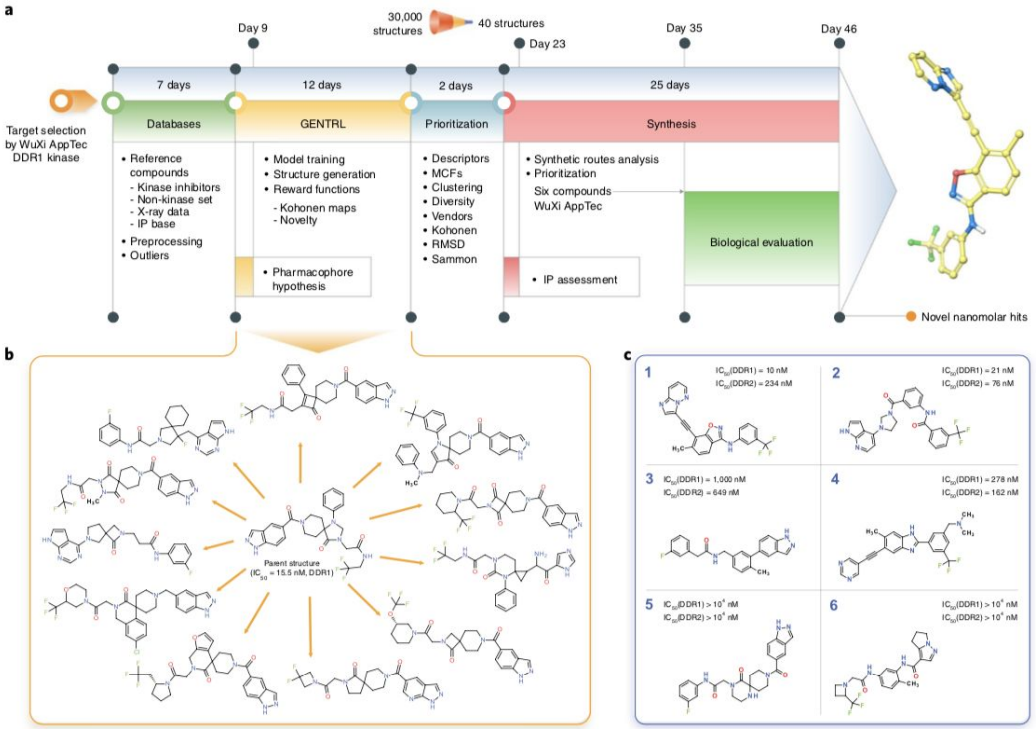


Fig. 1 | GENTRL model design, workflow, and nanomolar hits. a, The general workflow and timeline for the design of lead candidates using GENTRL. IP, intellectual property. **b**, Representative examples of generated structures compared to the parent DDR1 kinase inhibitor. **c**, Generated compounds with the highest inhibition activity against human DDR1 kinase.

Drug repurposing/repositioning

Drug Discovery Today
Volume 20, Issue 8, August 2015, Pages 1027-1034

Definitions

Review
Post-screen

Drug repositioning and repurposing: terminology and definitions in literature

Joris Langedijk [1, 2], Aukje K. Mantel-Teeuwisse [1], Diederick S. Slijkerman [2], Marie-Hélène D.B. Schutjens [1, 3]

Trending terms in represent novel drug development strategies.

- drug repositioning
- drug repositioning,
- drug repurposing,
- drug reprofiling,
- drug redirecting
- drug rediscovery

definition range from brief and general to extensive and specific

Drug repurposing/repositioning

nature reviews drug discovery

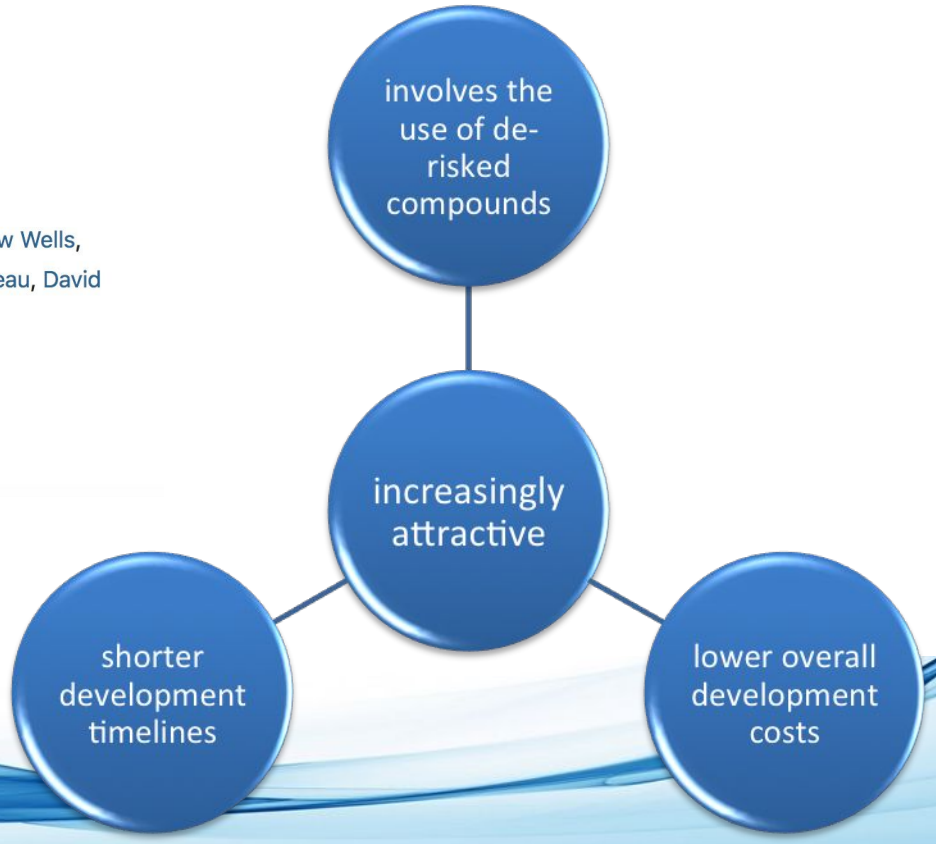
Various data-driven and experimental approaches have been suggested for the identification of repurposable drug candidates; however, there are also major technological and regulatory challenges.

Published: 12 October 2018

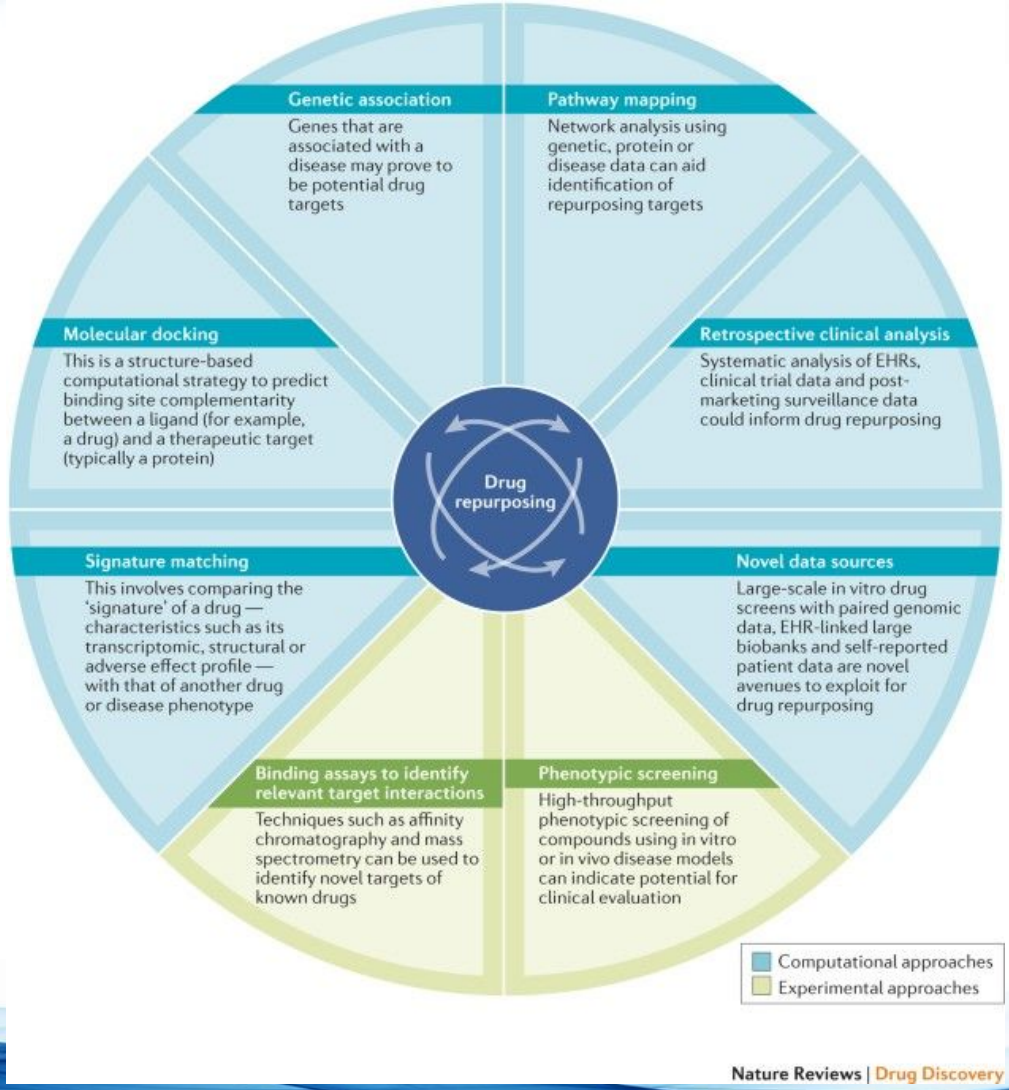
Drug repurposing: progress, challenges and recommendations

Sudeep Pushpakom, Francesco Iorio, Patrick A. Eyers, K. Jane Escott, Shirley Hopper, Andrew Wells, Andrew Doig, Tim Guilliams, Joanna Latimer, Christine McNamee, Alan Norris, Philippe Sanseau, David Cavalla & Munir Pirmohamed

Nature Reviews Drug Discovery **18**, 41–58 (2019) | Cite this article



Drug repurposing/repositioning



Drug repurposing/repositioning

Oncology appropriate for DRR:
a single mechanism or biomarker is frequently linked to a broad range of tumor types.

Merck's Keytruda® (pembrolizumab) which was first approved for advanced melanoma, now it is approved for 14 cancer types, including lung cancer and lymphoma. The company is constantly evaluating Keytruda for more cancers, such as triple-negative breast cancer.

Due to its similar PD-1-based mechanism of action (MOA), Bristol-Myers Squibb's (BMS) Opdivo® (nivolumab) is currently approved for 10 cancer types and the company is continuing to investigate the drug's efficacy for other indications.

Novartis' drug Arzerra (ofatumumab), a monoclonal antibody that targets the CD20 protein, was initially developed to treat chronic lymphocytic leukemia (CLL). However, clinical studies are currently underway to determine its effectiveness as a treatment for adult patients with relapsing forms of multiple sclerosis (MS).

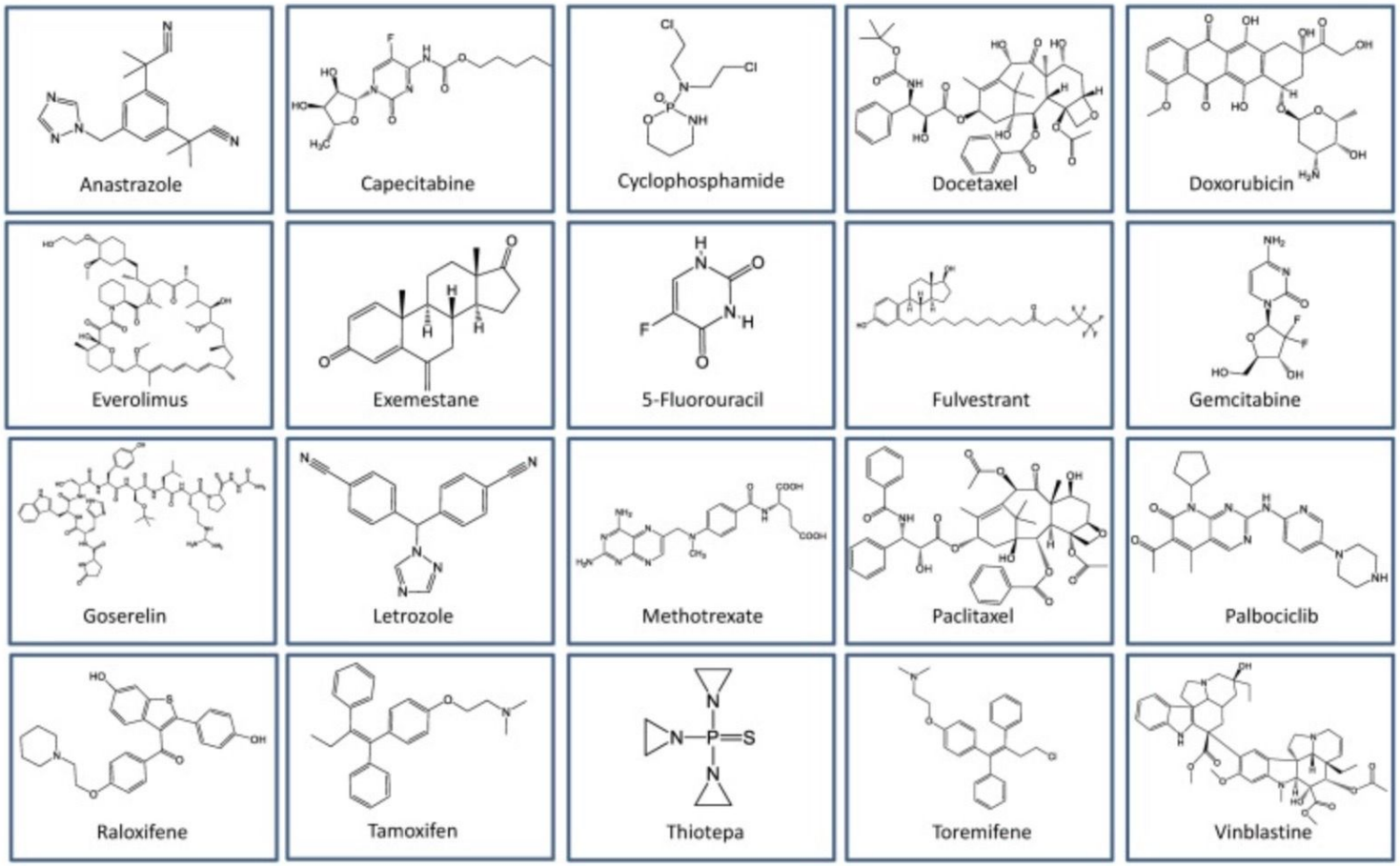
Drug repurposing/repositioning

Semin Cancer Biol. 2021 Jan; 68: 8–20.
Published online 2019 Sep 21. doi: 10.1016/j.semcancer.2019.09.012
PMCID: PMC7128772
PMID: 31550502

Drug repurposing for breast cancer therapy: Old weapon for new battle

Sadhna Aggarwal,[a] Sumit Singh Vern

Author information Article notes



Drug repurposing/repositioning

Drug			Breast cancer stage	Mechanism	Original indication
Category	**Chemical name**	**Commercial name**			
Alkylating agent	Cyclophosphamide	Cytoxan, Clafen, Neosar	Early and advanced	Inhibits DNA replication by damaging genetic material of the cell	As immuno-modulator in autoimmune diseases
	Thiotepa	Thioplex, Tespa, Thiophosphoamide, TSPA, Tepadina	Early and advanced		Immunosuppressant
Anthracyclins	Doxorubicin	Adriamycin, Caelyx, Rubex	Advanced	DNA intercalation	Antibiotic from *Streptomyces peucetius* bacterium
Antimetabolite	Capecitabine	Xeloda	Metastatic and advanced	False building block incorporation during cell growth	Colon cancer
	Fluorouracil	Adrucil, Carac	Early, advanced and metastatic		Keratoacanthomas, actinic keratosis, and skin warts
	Gemcitabine	Gemzar	Metastatic and advanced		Anti-viral drug
	Methotrexate	Mexate, Folex, Rheumatrex	Early and advanced		Leukemia

Drug repurposing/repositioning

CDK 4/6 inhibitor	Palbociclib, Palbonix	Ibrance	ER+, PR+, HER2-, advanced	Interferes with cell cycle	CDK 4/6 inhibitor
HT-SERM	Tamoxifen	Nolvadex, Apo-Tamox, Tamifen, Soltamox	ER+, PR+, advanced	Binds to ER	Albright syndrome, ovulation induction
	Toremifene	Fareston	ER+, PR+		Infertility with an ovulatory disorders
	Raloxifene	Evista	ER+, PR+		Osteoporosis in postmenopausal women
HT-Aromatase inhibitor	Exemestane	Aromasin	ER+, PR+	Lowers estrogen amount	Ovulation induction
	Letrozole	Femara	ER+, PR+, early and advanced		Ovulation induction
	Anastrazole	Arimidex	ER+, PR+, advanced		Ovulation induction
HT-SERD	Fulvestrant	Faslodex	ER+, PR+, HER2-, advanced	ER degradation	Antiestrogen
HT-LHRH agent	Goserelin	Zoladex	ER+, PR+, early	Reduces amount of estrogen	Prostate cancer, uterine fibroids, assisted reproduction
mTOR inhibitor	Everolimus, Votubia, Evertor	Afinitor	HER2+, HER2-	Interferes with mTOR kinase	Immunosuppressant during organ transplants, wound healing
Mitotic inhibitor	Docetaxel	Taxotere	Early and advanced	Interferes with cell division	Hormone-refractory prostate cancer
	Paclitaxel	Taxol, Onxol	Early and advanced		Ovarian cancer, atrial restenosis
	Vinblastine	Velban, Velsar, Adria, Velbe	Advanced	Interferes with genes	Hodgkin lymphoma, non-Hodgkin's

Drug repurposing/repositioning

Journal List › Oncoscience › v.2(6); 2015 › PMC4506360

Oncoscience

Oncoscience. 2015; 2(6): 576–580. PMCID: PMC4506360
Published online 2015 Jun 30. doi: 10.18632/oncoscience.173 PMID: 26244164

Challenges and perspective of drug repurposing strategies in early phase clinical trials

Shumei Kato,[1] Stacy L. Moulder,[2] Naoto T. Ueno,[2] Jennifer J. Wheler,[1] Funda Meric-Bernstam,[1] Razelle Kurzrock,[3] and Filip Janku[1]

dosage required for the treatment of a novel disease usually differs from that of its original target disease - > discovery begins from Phase I

finding of new formulation and distribution mechanisms of existing drugs to the novel-disease-affected areas

patent right issues

leverage and critically evaluate existing evidence and to investigate the efficacy/ effectiveness and safety of drug for potential repurposing

pre-clinical, clinical and observational research need to generate complementary information

DD/DRR in oncology

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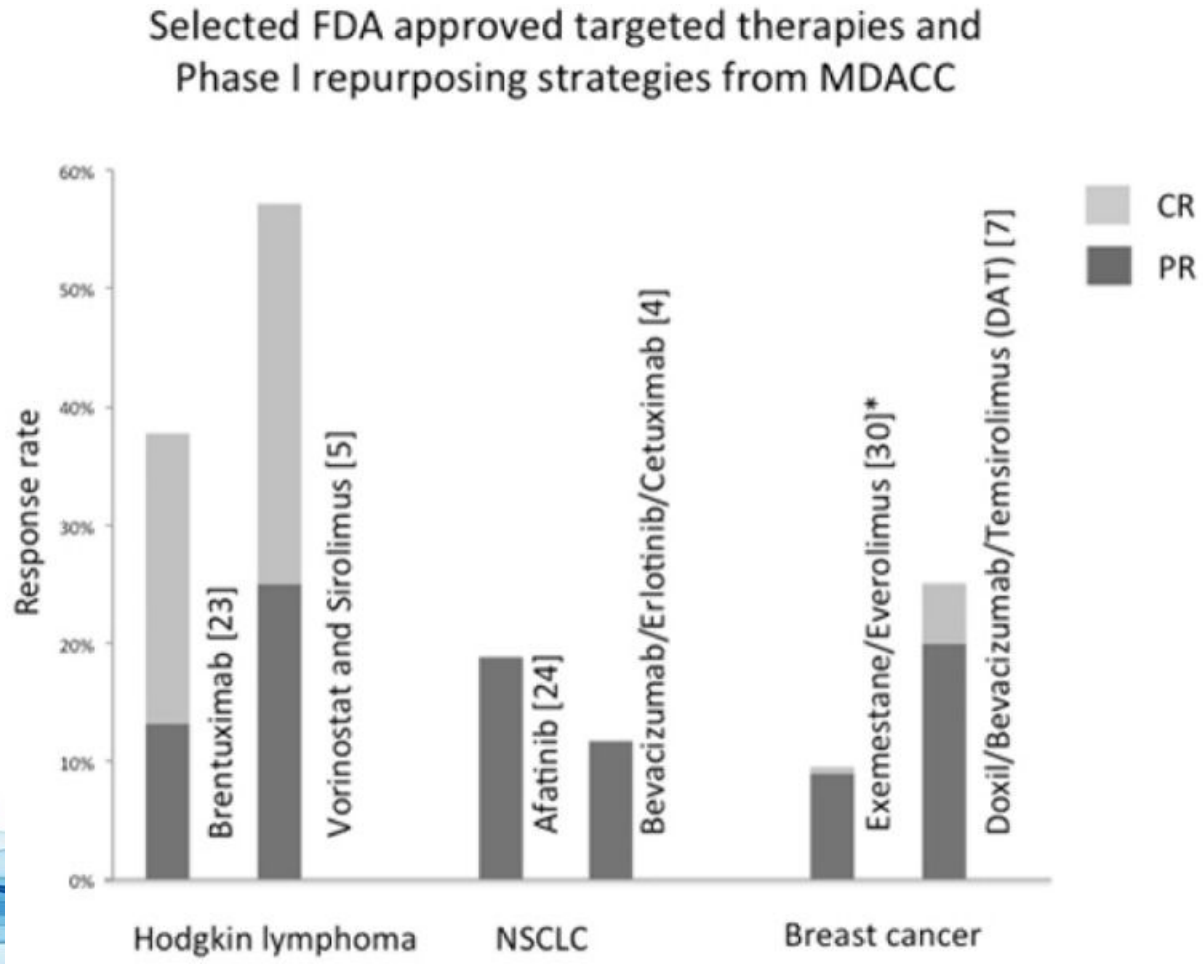
Historically, the expected response rate in Phase I trials with unselected populations of patients has ranged from 4% to 11%.

However, with recent advances in targeted therapies and molecular matching, the response rates in Phase I trials have ranged from 19% to 77%, and some agents that demonstrated high response rates are now FDA approved.

Even in heavily pretreated patients, drug repurposing combination regimens have yielded response rates ranging 12% to 57%.



Drug repurposing/repositioning

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A Phase I clinical trial combining liposomal doxorubicin, bevacizumab, and temsirolimus (DAT) for patients with advanced cancers was designed to test the preclinical rationale that resistance to anthracyclines is driven through upregulation of hypoxia-inducible factor alpha (HIF-1α), which promotes angiogenesis and tumor survival. Thus inhibiting angiogenesis, such as with the VEGF inhibitor bevacizumab, may overcome anthracycline resistance. However, resistance to bevacizumab is also driven by upregulation of HIF-1α. Addition of temsirolimus, a potent inhibitor of mTOR and consequently HIF-1α, can overcome this resistance.

Drug repurposing/repositioning

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During the dose-escalation phase MD Anderson team noticed remarkable activity in several distinct tumor types, including **metaplastic breast cancer (MpBC)**.

Despite the aggressive nature of this cancer:
2 responses (1 complete [CR],1 partial response [PR]) in 5 patients with treatment-refractory MpBC.

In extended observation, objective responses in 5 of the 12 patients with MpBC (42%, 2 CR and 3 PR) and stable disease (SD) > 6 months in another 6 [50%].

Drug repurposing/repositioning

Drug repurposing against breast cancer by integrating drug-exposure expression profiles and drug–drug links based on graph neural network

Chen Cui, Xiaoyu Ding, Dingyan Wang, Lifan Chen, Fu Xiao, Tingyang Xu, Mingyue Zheng ✉, Xiaomin Luo ✉, Hualiang Jiang, Kaixian Chen

Bioinformatics, btab191, https://doi.org/10.1093/bioinformatics/btab191

predict new drugs for breast cancer, outperforming previous state-of-the-art approaches and some classic machine learning methods

- graph neural network model GraphRepur based on GraphSAGE for drug repurposing against breast cancer
- integrated two major classes of computational methods, drug network-based and drug signature-based
- differentially expressed genes of disease, drug-exposure gene expression data and the drug–drug links information were collected -> extracting the drug signatures and topological structure information contained in the drug relationships

Drug repurposing/repositioning

Review

Drug Repurposing for Triple-Negative Breast Cancer

Marta Ávalos-Moreno [1,†], Araceli López-Tejada [1,2,†], Jose L. Blaya-Cánovas [1,2], Francisca E. Cara-Lupiañez [1,2], Adrián González-González [1,2], Jose A. Lorente [1,3], Pedro Sánchez-Rovira [2] and Sergio Granados-Principal [1,2,*]

novel and inclusive classification of DRR approaches whereby drug repurposing can be achieved in silico: structure-based, transcriptional signatures-based, biological networks-based, and data-mining-based

the most relevant research, both at preclinical and clinical settings, aimed at repurposing pre-existing drugs to treat TNBC on the basis of molecular mechanisms and signaling pathways such as androgen receptor, adrenergic receptor, STAT3, nitric oxide synthase, or AXL

ability and relevance of cancer stem cells (CSCs) to drive tumor aggressiveness and

poor clinical outcome -> focus on those molecules repurposed to specifically target this cell population to tackle recurrence and metastases associated with the progression of TNBC

Analytical drug discovery tools

Based on deep learned transcriptomics-, proteomics-, blood biochemistry-based biomarkers of multiple diseases, predictors of alternative therapeutic uses of multiple drugs and analytical tools for high-throughput screening.

The measurement of physicochemical properties at an early phase of drug discovery and development is crucial to reduce attrition rates due to poor biopharmaceutical properties.,

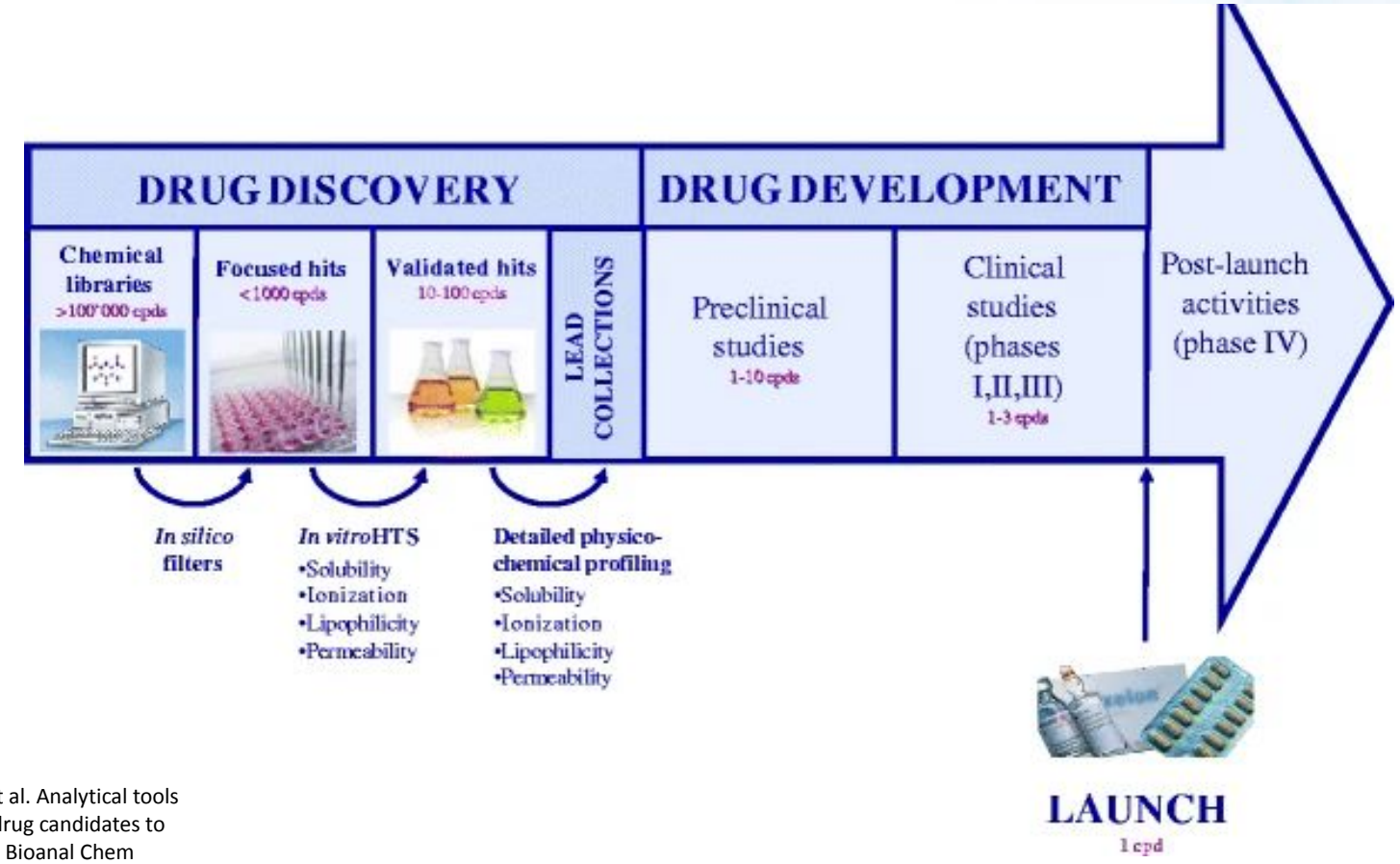
- lipophilicity
- solubility
- Ionization
- permeability

mandatory to predict the pharmacokinetic behavior of NCEs.

Due to the high number of NCEs, the analytical tools used to measure these properties are automated and progressively adapted to high-throughput technologies.

Henchoz, Y., Bard, B., Guillarme, D. et al. Analytical tools for the physicochemical profiling of drug candidates to predict absorption/distribution. Anal Bioanal Chem

Analytical drug discovery tools



Henchoz, Y., Bard, B., Guillarme, D. et al. Analytical tools for the physicochemical profiling of drug candidates to predict absorption/distribution. Anal Bioanal Chem

Clinical trials simulation

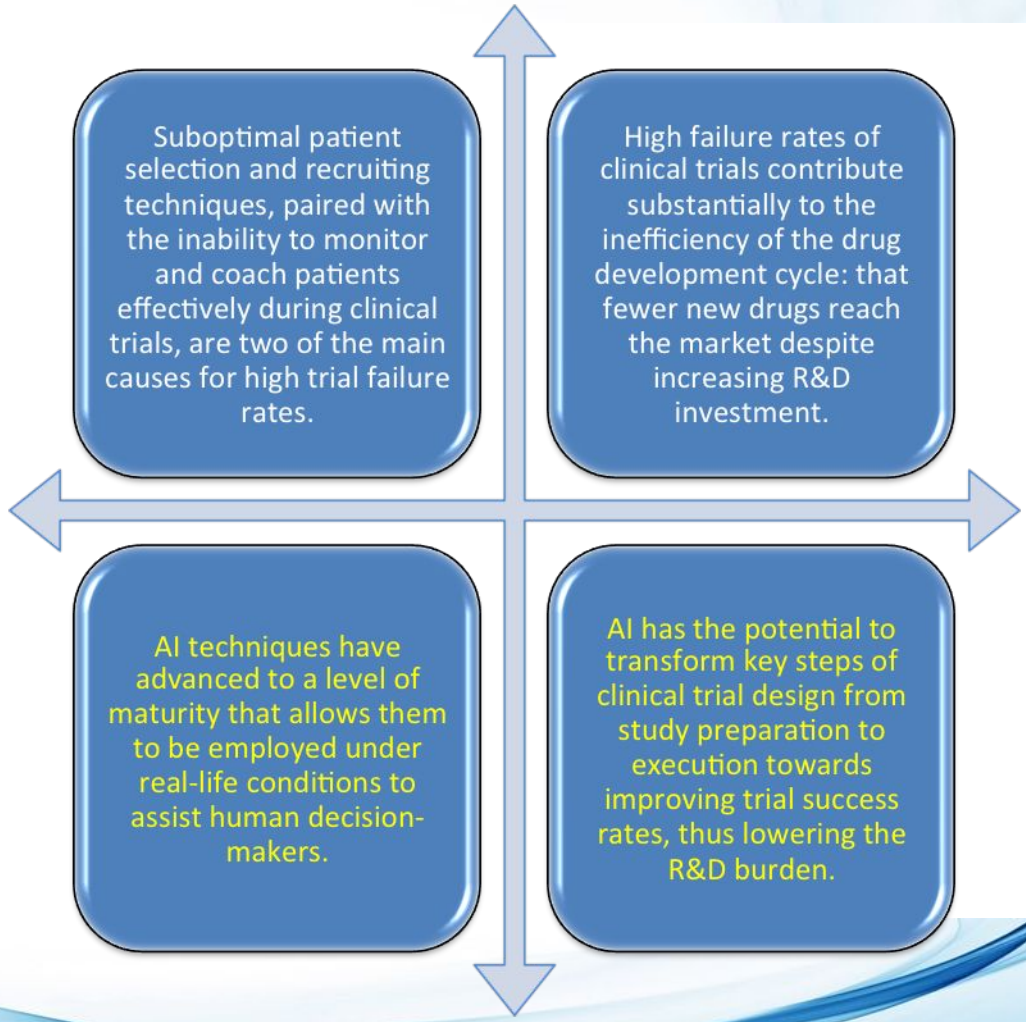
In silico + in vitro and in vivo

Trends in Pharmacological Sciences
Volume 40, Issue 8, August 2019, Pages 577-591

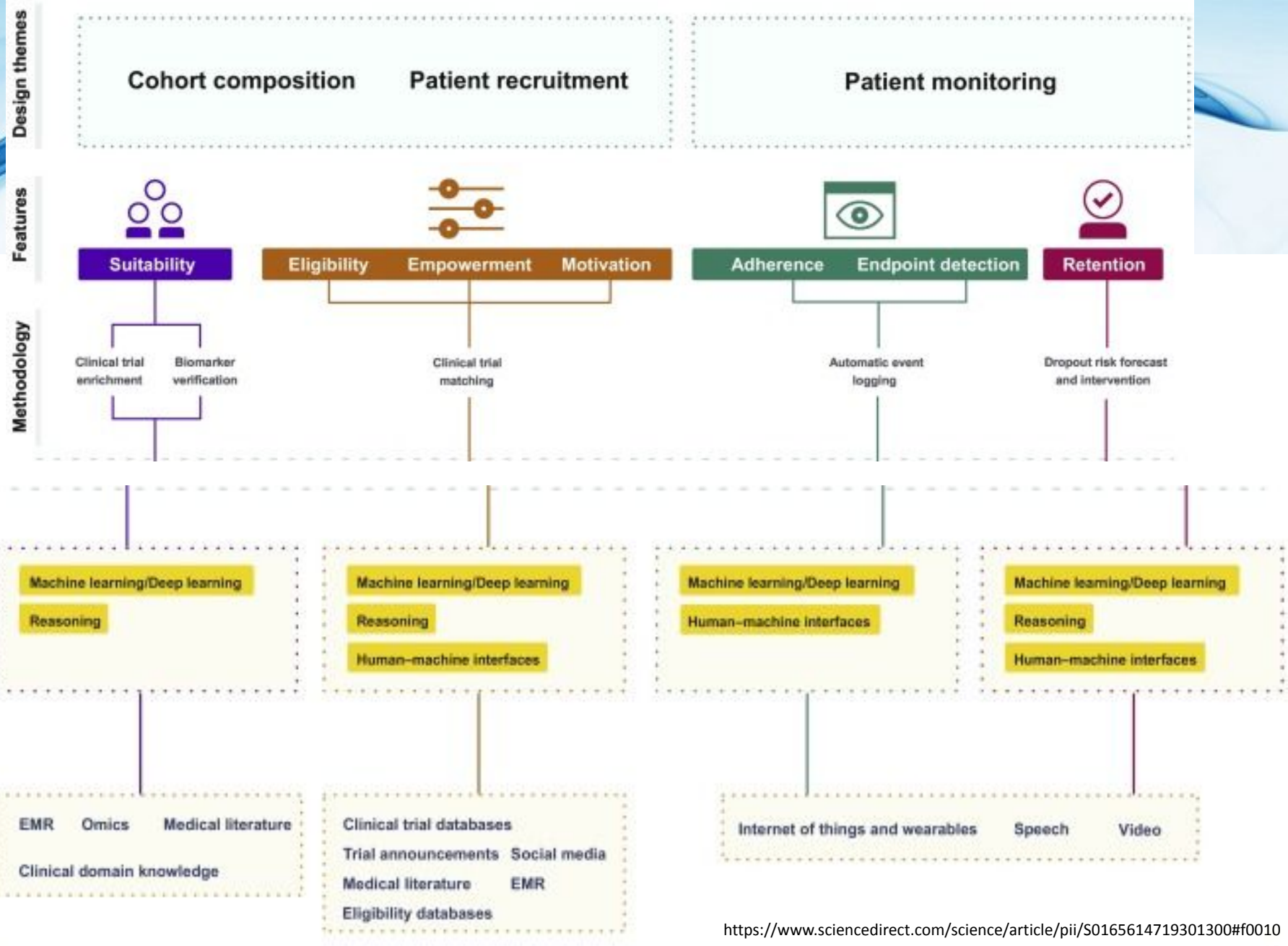
Review
Special Issue: Rise of Machines in Medicine

Artificial Intelligence for Clinical Trial Design

Stefan Harrer [1], Pratik Shah [2], Bhavna Antony [1], Jianying Hu [3]



Clinical trials simulation



https://www.sciencedirect.com/science/article/pii/S0165614719301300#f0010

Clinical trials simulation

Therapies
Volume 59, Issue 3, May–June 2004, Pages 297-304

PHARMACOLOGIE CLINIQUE

Clinical Trial Simulation in Drug Development

Pascal Girard [1], Michel Cucherat [2], David Guez [3]
Participants in Round Table No. 2, Giens XIX

Utilizes massive amounts of data about the targets, diseases, clinical trials, and even scientists involved with the study at the preclinical and clinical stages.

Prospective validation is the best way to predict the outcomes of clinical trials.

A reduction in the number of failed clinical development projects, the number of negative phase II and III clinical trials, or in just their cost and duration, are among the expected benefits of modelling and simulation in clinical drug development.

https://www.sciencedirect.com/science/article/pii/S0165614719301300#f0010

Clinical trials simulation

nature › scientific reports › articles › article

Article | Open Access | Published: 10 December 2019

Virtual clinical trials identify effective combination therapies in ovarian cancer

Emilia Kozłowska, Tuulia Vallius, Johanna Hynninen, Sakari Hietanen, Anniina Färkkilä ✉ & Sampsa Hautaniemi ✉

Scientific Reports **9**, Article number: 18678 (2019) | Cite this article

https://www.sciencedirect.com/science/article/pii/S0165614719301300#f0010

Clinical trials simulation

ELSEVIER

European Journal of Cancer

Volume 85, November 2017, Pages 78-85

Original Research

Clinical trial simulations in paediatric oncology: A feasibility study from the Innovative Therapies for Children with Cancer Consortium

Clinical trials simulation

Optimizing drug development in oncology by clinical trial simulation: Why and how? FREE

Jocelyn Gal ✉, Gérard Milano, Jean-Marc Ferrero, Esma Saâda-Bouzid, Julien Viotti, Sylvie Chabaud, Paul Gougis, Christophe Le Tourneau, Renaud Schiappa, Agnes Paquet ... Show more

This in silico medicine opens the way to the P4 medicine: predictive, preventive, personalized and participatory.

Drug activity modeling coupled with disease modeling, optimal use of medical data and increased computing speed should allow leap forward.

The realization of CTS requires not only bioinformatics tools to allow interconnection and global integration of all clinical data but also a universal legal framework to protect the privacy of every patient.

Clinical trials simulation

Simulation Modeling of Cancer Clinical Trials: Application to Omitting Radiotherapy in Low-risk Breast Cancer FREE

Jinani Jayasekera ✉, Yisheng Li, Clyde B Schechter, Reshma Jagsi, Juhee Song, Julia White, George Luta, Judith-Anne W Chapman, Eric J Feuer, Richard C Zellars

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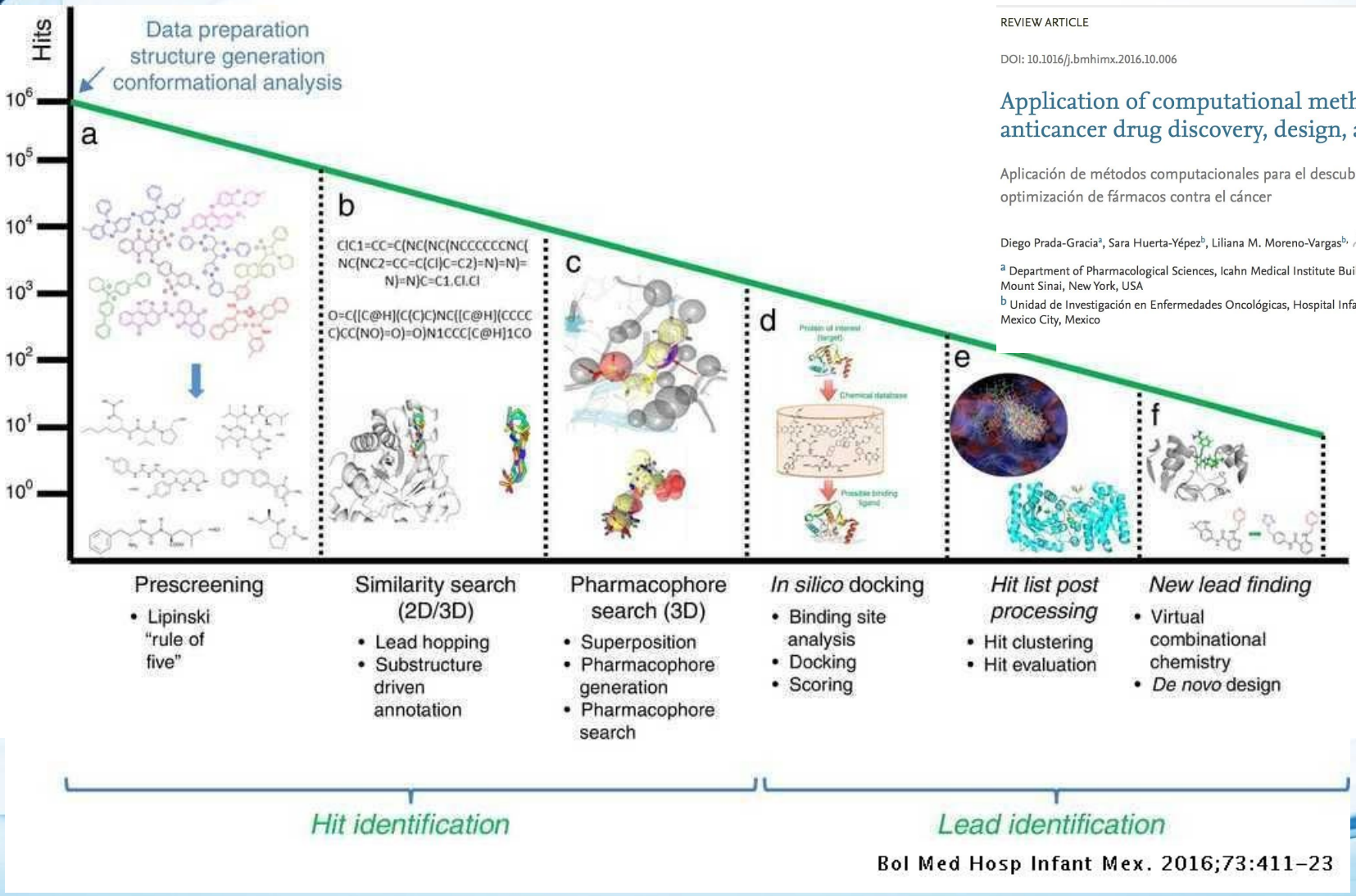
A paradigm shift is necessary to bring the benefits of CTS-based drug development to cancer patients, in which biomarkers and prognostic markers of OS are assessed to predict treatment outcome and disease progression.

Future?



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REVIEW ARTICLE

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Application of computational methods for anticancer drug discovery, design, and optimization

Aplicación de métodos computacionales para el descubrimiento, diseño y optimización de fármacos contra el cáncer

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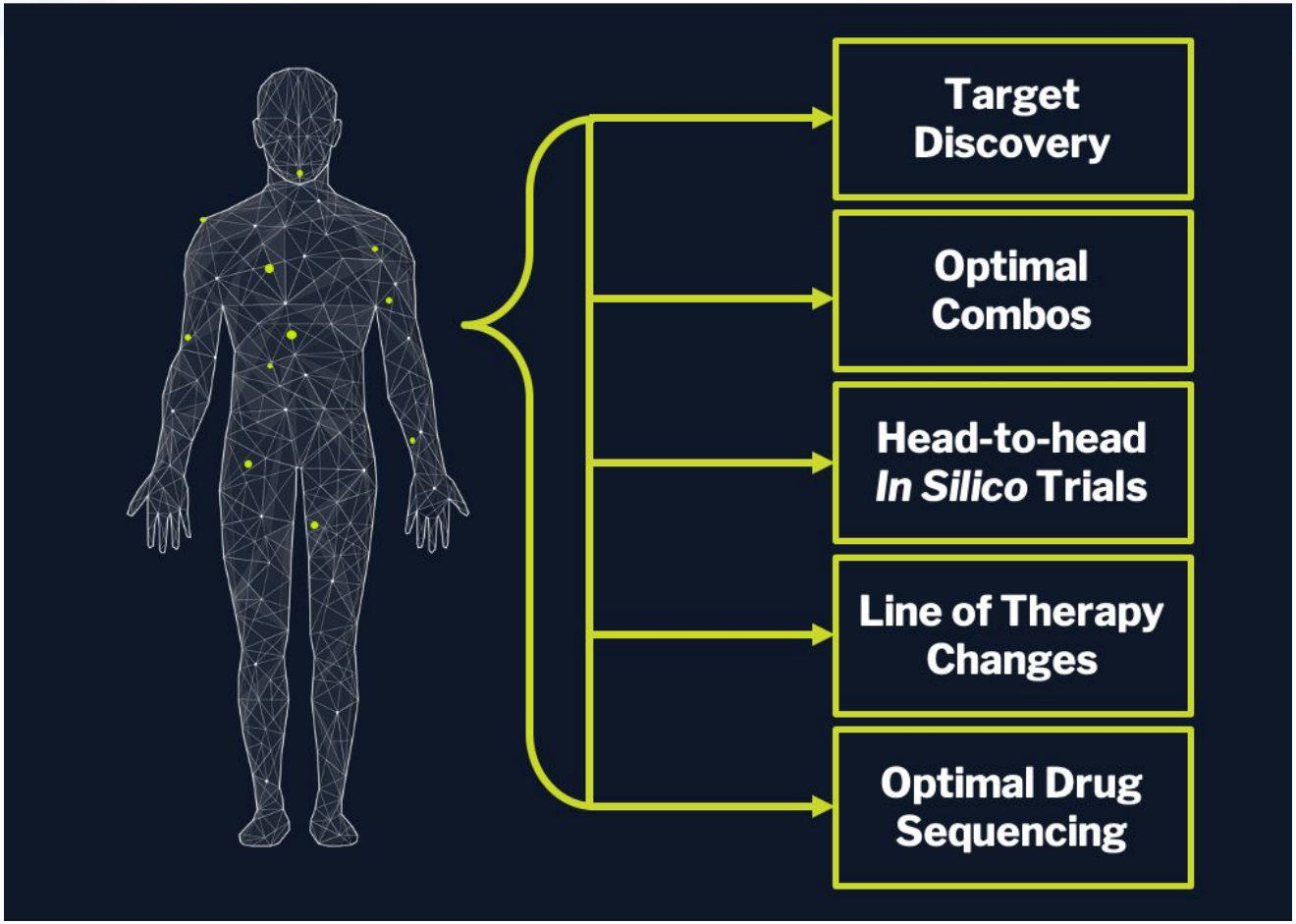
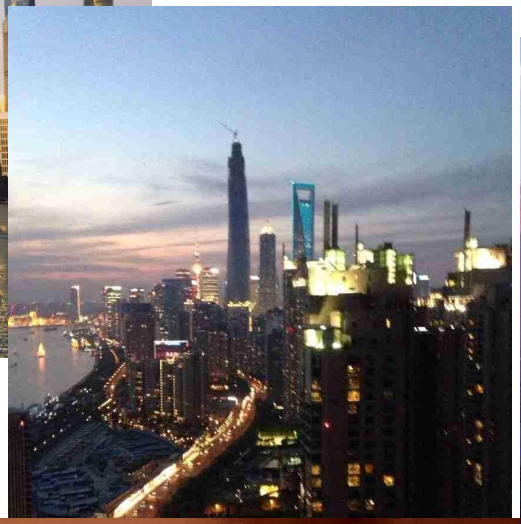
Future?



https://www.gnshealthcare.com/gemini-in-silico-patient/

Thank you



Thank you

Never tire to study
and to teach others.

学而不厌
诲人不倦
孔子