Using AI to Improve the Safety of New Drug Candidates

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Streamlining Drug Discovery

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Outline

• Why safety?
• What are key causes of safety failures?
• How will artificial intelligence help?
• Where are the key gaps?
Safety Failures in the Clinic

CD28 Agonist  FAAH Inhibitor  CETP Inhibitor  COX2 Inhibitor

Preclinical  Phase I  Phase II  Phase III  Post-Approval

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5R framework increased the R&D productivity

Impact of a five-dimensional framework on R&D productivity at AstraZeneca

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What is Causing Safety Failures

Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework.

Safety causes for candidate drug terminations

Numerous causes of safety attrition, predominantly compound related

More likely to succeed when high confidence in preclinical safety

Build confidence in safety at the point of design

Once a chemical is synthesized, its properties are, for the most part, fixed. All that remains is to discover what they are.
Machine Learning and AI

Since an early flush of optimism in the 1950’s, smaller subsets of artificial intelligence - first machine learning, then deep learning, a subset of machine learning - have created ever larger disruptions.
So what’s the big deal about AI?

- Artificial Intelligence has the capability to transform drug safety

- Need to separate the reality from the hype

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Areas for investment in Artificial Intelligence

AI is becoming the foundation of accelerated, large scale computational analysis and integration

Molecular Design
maximize Ti through improved modelling, SAR, in silico screens

Target Selection
Literature and competitor information mining; in house pharmacology

Translation
Improved understanding of the translation of preclinical signals to patient populations

Improved hazard detection
Early, fast, better detection of organ safety risks; 3 R’s

The impact of AI will come from big data analysis, modeling and image analysis

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Target Identification & Selection

- Choose the right target
- Understand the broader risks of modulating a target
- Using AI for literature and competitive intelligence mining by NLP
- Drug target liability scoring from knowledge graphs vs major organs according to patient context
Hazard Detection

Collage of some medical imaging applications in which deep learning has achieved state-of-the-art results.

From top-left to bottom-right:

1. mammographic mass classification
2. segmentation of lesions in the brain,
3. leak detection in airway tree segmentation,
4. diabetic retinopathy classification
5. prostate segmentation,
6. nodule classification,
7. breast cancer metastases detection,
8. skin lesion classification
9. bone suppression
AI in Pathology Studies

- Different approaches for different problems
- Consistency over large data sets and studies
- Big data generation will enable insights that are greater than the sum of the parts
Using AI in Pathology

• ~80% of tissue slices read from a study are “normal”

• Using image analysis and Deep Learning it will be possible to reduce the time taken to read a study

• Data storage, however, will be non-trivial. Estimate 1.5TB of images per year.
Translation

• The ability to put the safety signals we see preclinically into context with knowledge of the patient
Artificial Intelligence in Drug Discovery

Productivity
- Prosecuting more projects without a linear increase in cost

Exploring more chemical space in the hunt for the **best** leads
- Greater opportunity for exploration over exploitation
Applications of AI in Molecular Design

What to make next?

De novo design

How to make it?

Synthesis planning
Molecular Design

- Drug discovery is a multi-parameter optimization problem
- Balance of efficacy/potency, ADME and safety

Need to find the optimum chemical space to work in
Therapeutic index is often uncertain

Find *productive* chemistry space early

The safety and efficacy of a drug candidate needs to be well balanced

Muller & Milton (2012). Nat Rev Drug Discovery

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Absorption-Distribution-Metabolism-Excretion (ADME)


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Key Gaps

Accurate prediction of human PK will lead to:

- Better understanding of clinical feasibility
- Better estimates of therapeutic index
- Better use of resources in producing clinic-ready material

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Summary

- Data, and the knowledge gained from it, are one of a company’s most valuable asset
- The volume of data generation is growing almost exponentially and is rapidly outstripping our capacity to digest all the information
- Artificial intelligence will enable us to exploit and maximize the value we get from our data
- Drug discovery is a multi-parameter problem that requires the ability to think in multiple dimensions
- Safety, ADME are as (more) important as efficacy/potency
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