Drug Discovery: History and Paradigms

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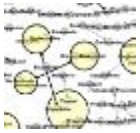
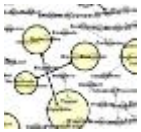
Based on slides by Prof. David Wild, 2013 edition of course.



Drug discovery history and paradigms: DSDHT context & relevance



DATA SCIENCE FOR DRUG DISCOVERY, HEALTH AND TRANSLATIONAL MEDICINE (DSDHT) INFO I-590

Q1 How can data science help researchers find new drugs and reuse old ones?

Module 5: The drug discovery process	Module 6: Bioinformatics introduction	Module 7: Bioinformatics and medicine	Module 8: Cheminformatics

Data science

Drug discovery paradigms

- **Empirical**
  - ~200k BCE+
- **Vitamins, vaccines & antibiotics**
  - ~1800+
- **Rational**
  - ~1960+
- **Integrative**
  - ~2010+

Context: Public health, science, medicine

Why care about history? All paradigms active *now*.

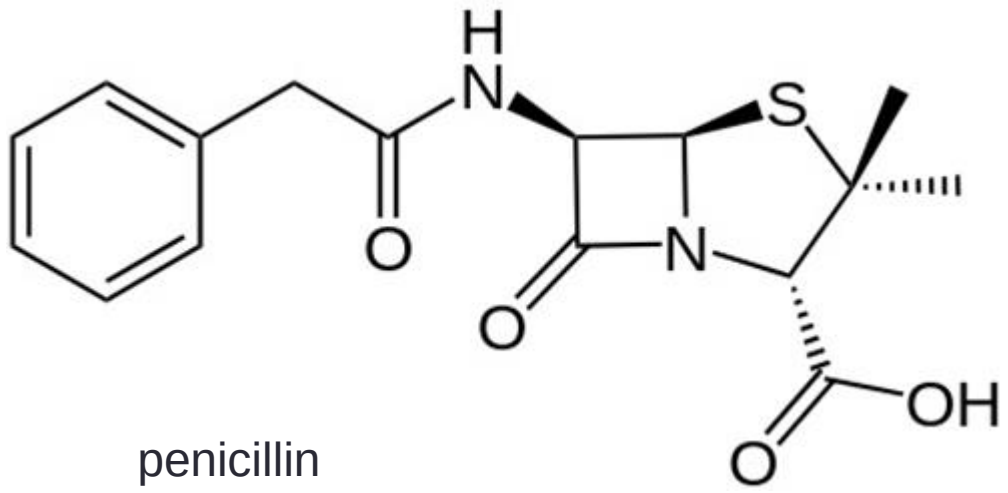
Drug discovery paradigms: Empirical

- **~200k BCE (human existence)**
- **754 - First pharmacy opened in Baghdad**
- **1800s – major pharmas, mass production**
- **Natural products, traditional medicines**
- **Limited disease scope: pain relief, infectious disease**

poppy flower, pods, seeds

Drug discovery paradigms: Vitamins, vaccines & antibiotics

- **~1800+**
- **Science: nutrition, immunology, microbiology**
- **Vitamin deficiency diseases: scurvy (C), pellagra (B3), beriberi (B1), rickets (D)**
- **Malnutrition, infectious diseases predominant risks**
- **Penicillin, polio vaccine & other "wonder drugs"**



penicillin

Drug discovery paradigms: Vitamins, vaccines & antibiotics

- **A few statistics**
  - **Black Death, a.k.a. Bubonic Plague**
    - **1340-1400**
    - **~100 million deaths, ⅓ European population**
  - **1918 influenza epidemic**
    - **~20 million deaths, ~1% world population.**
  - **Life expectancy**
  - **Infant mortality (death in first year)**

Drug discovery paradigms: Vitamins, vaccines & antibiotics

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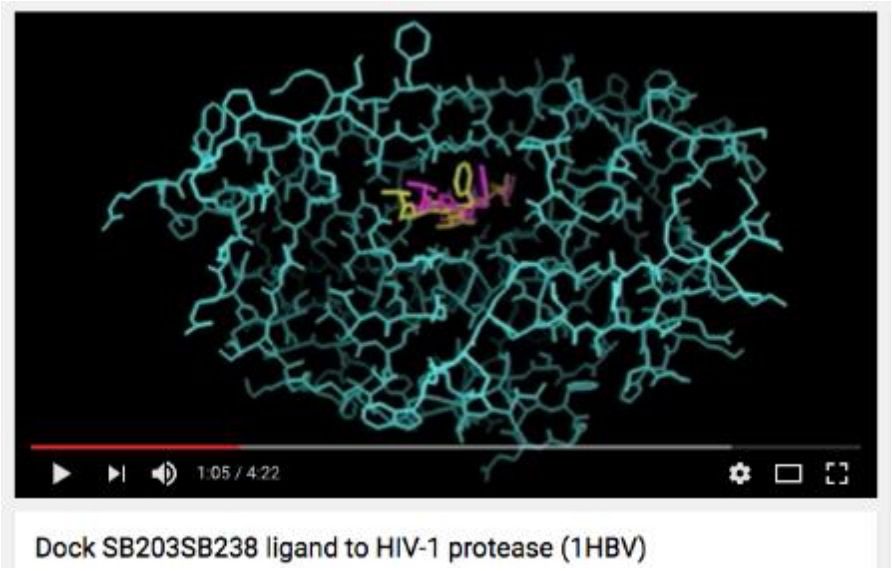
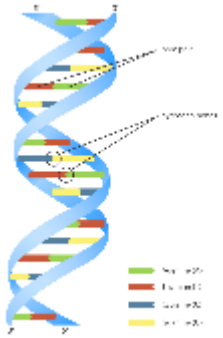
Country	Year	Life expectancy	Infant mortality
Canada	1900	48	18.7%
	1950	68	4.1%
	2000	79	0.5%
China	1900	32	
	1950	40	19.5%
	2000	72	3.0%
USA	1900	49	
	1950	68	3.3%
	2000	77	0.7%

data from gapminder.org

Drug discovery paradigms: Rational

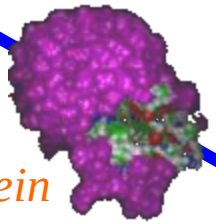
- **~1960+**
- **Scientific: molecular biology, computer science**
- **“Lock and key” concept: target protein, selective drug**
- **Some big successes (e.g. HIV)**
- **Expanded disease scope: metabolic, cancer, mental**





Rational Drug Discovery "Pipeline"

Identify disease



Isolate protein involved in disease (2-5 years)

Find a drug effective against disease protein (2-5 years)

Preclinical testing (1-3 years)

Formulation & Scale-up

File IND

Human clinical trials (2-10 years)

File NDA

FDA approval (2-3 years)

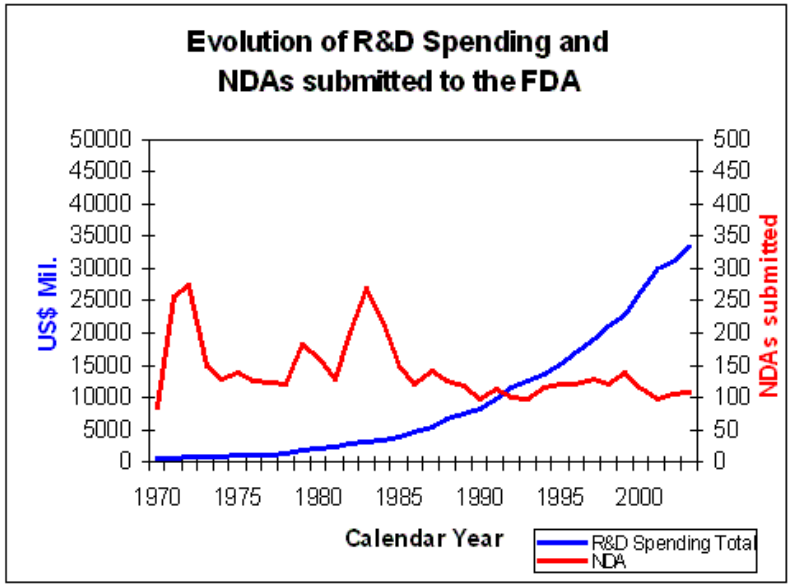
DISCOVERY

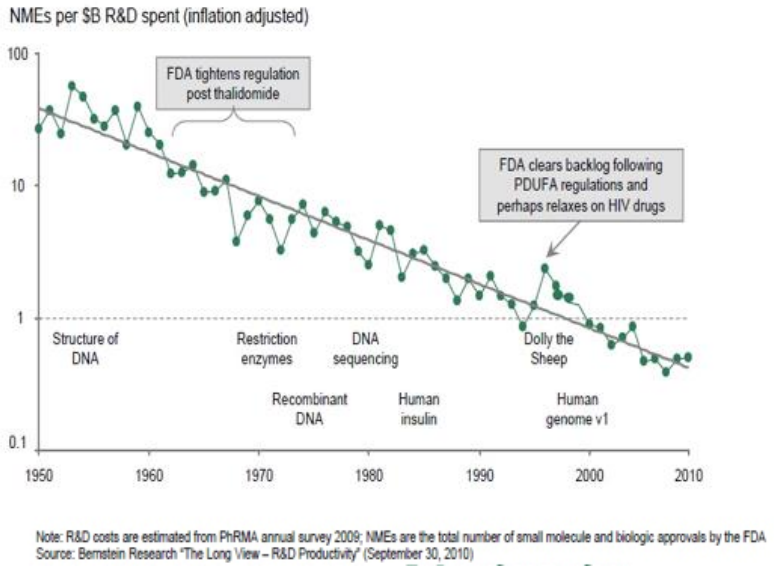
DEVELOPMENT

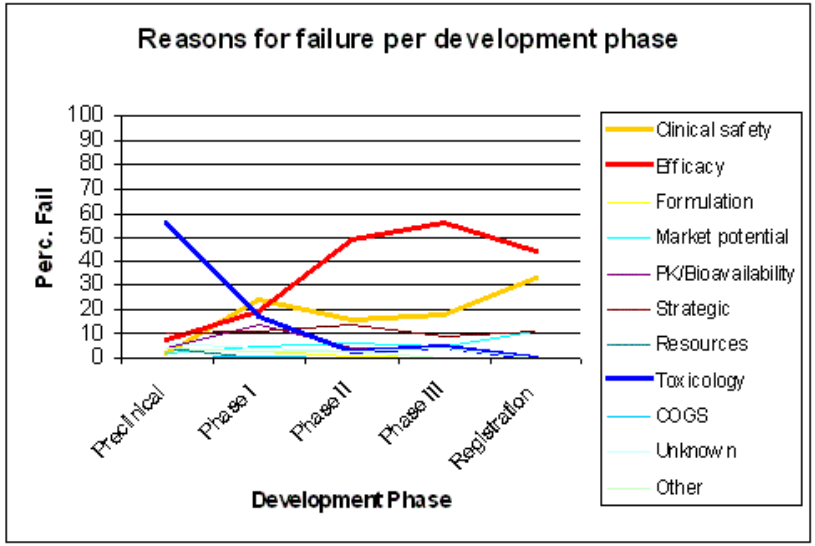
CLINICAL TRIALS

MARKETING >>

Stagnation in new drug therapies







Graphs taken from Vanosta.be

Filling the Prescription

Novel drugs recently approved and in the pipeline

Drug	Target	Timing	Maker	Estimated peak yearly sales
Benlysta	Lupus	2011*	GlaxoSmithKline, Human Genome Sciences	$3.2 billion
Yervoy	Metastatic melanoma	2011*	Bristol-Myers Squibb	$2.8
Victrelis	Hepatitis C	2011*	Merck	$1.2
Xarelto	Blood clots	2011*	Bayer, Johnson & Johnson	$4.3
crizotinib	Lung cancer	2011†	Pfizer	$2.0
vemurafenib	Metastatic melanoma	2011†	Roche, Daiichi Sankyo	$1.0
tofacitinib	Rheumatoid arthritis	2012**	Pfizer	$2.2
bardoxolone	Chronic kidney disease	2013**	Abbott, Reata	$1.1
dalcetrapib	Cardiovascular risk	2014**	Roche	$4.0
mericitabine	Hepatitis C	2014††	Roche, Pharmasset	$1.3
anti-BAFF antibody	Rheumatoid arthritis, lupus	2015**	Eli Lilly	$1.2
darapladib	Atherosclerosis	2016**	GlaxoSmithKline	$3.8

Note: Novel drugs are those that work differently from existing drugs or are aimed at poorly treated diseases.
*Approved †Submitted to FDA for review **In final clinical trials ††In next-to-final trials
Sources: Credit Suisse; the companies

Drug Withdrawals

Drug Name	Year	Country	Remarks
Trovafloxacin (Trovan)	2000	European Union,	Risk of liver failure
Alosetron (Lotronex)	2000	US	Serious gastrointestinal adverse events; ischemic colitis; severe constipation.
Cisapride (Propulsid)	2000	US	Risk of fatal cardiac arrhythmias
Phenylpropanolamine(Propagest	2000	Canada, US	Hemorrhagic stroke.
Troglitazone (Rezulin)	2000	US, Germany	Hepatotoxicity
Cerivastatin (Baycol, Lipobay)	2001	US	Risk of rhabdomyolysis
Rapacuronium (Raplon)	2001	Multiple	Risk of fatal bronchospasm
Sparfloxacin	2001	US	QT prolongation and phototoxicity.
Kava Kava	2002	Germany	Hepatotoxicity.
Levomethadyl acetate	2003	US	Cardiac arrhythmias and cardiac arrest.
Bezitramide	2004	Netherlands	Fatal overdose.
Co-proxamol (Distalgesic)	2004	UK	Overdose dangers.
Dofetilide	2004	Germany	Drug interactions, prolonged QT.
Rofecoxib (Vioxx)	2004	Worldwide	Risk of myocardial infarctionand stroke
Valdecoxib (Bextra)	2004	US	Risk of heart attack and stroke.
Hydromorphone (Palladone, ext	2005		High risk of overdose, extended release version with alcohol.
Thioridazine (Melleril)	2005	Germany, UK	Severe cardiac arrhythmias
Alatrofloxacin	2006	Worldwide	Liver toxicity; serious liver injury leading to liver transplant; death.
Gatifloxacin	2006	US	Increased risk of dysglycemia.
Ximelagatran (Exanta)	2006	Germany	Hepatotoxicity
Clobutinol	2007	Germany	Ventricular arrhythmia, QT-prolongation.
Lumiracoxib (Prexige)	2007	Worldwide	Liver damage
Nefazodone	2007	Multiple	Hepatotoxicity
Pergolide (Permax)	2007	US	Risk for heart valve damage.
Tegaserod (Zelnorm)	2007	US	Risk for heart attack, stroke, and unstable angina.
Aprotinin (Trasylol)	2008	US	Increased risk of death.
Rimonabant (Acomplia)	2008	Worldwide	Risk of severe depression and suicide.
Efalizumab (Raptiva)	2009	Germany	Increased risk of progressive multifocal leukoencephalopathy.
Propoxyphene (Darvocet/Darvo	2010	Worldwide	Increased risk of heart attacks and stroke.
Gemtuzumab ozogamicin(Mylo	2010	US	No improvement in clinical benefit; risk for death.
Ozogamicin	2010	US	No improvement in clinical benefit; risk for death; veno-occlusive disease.
Rosiglitazone (Avandia)	2010	Europe	Risk of heart attacks and death.
Sibutramine (Reductil/Meridia)	2010	Multiple	Increased risk of heart attack and stroke.
Sitaxentan	2010	Germany	Hepatotoxicity.
Tetrazepam	2013	European Union	Serious cutaneous reactions.

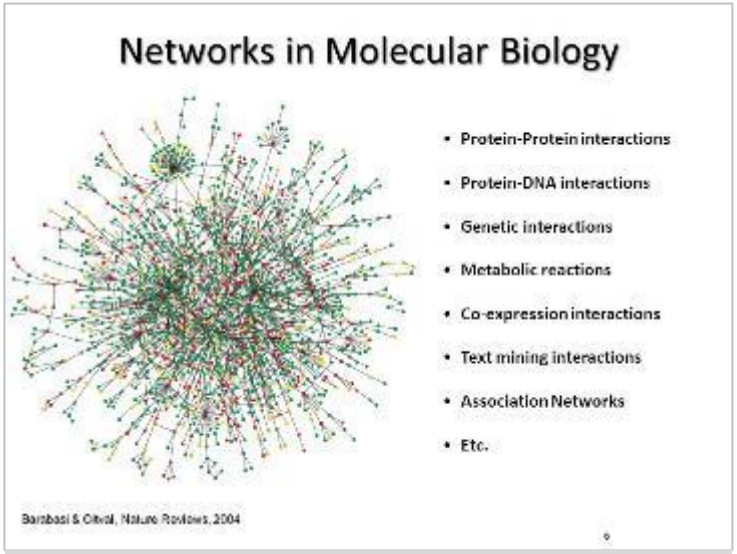
Since 2000, due to safety and efficacy alerts.

Evidence of flawed system?

Withdrawal information taken from http://en.wikipedia.org/wiki/List_of_withdrawn_drugs.

Drug discovery paradigms: Integrative

- **~2010+**
- **Science and technology**
  - **Systems biology**
  - **Informatics**
  - **Data science**
- **Data integration**
  - **Molecular**
  - **Clinical**
  - **Genomic**
  - **Bibliological**
  - **Epidemiological**
- **Integrates other paradigms**



Barabasi and Oltvai, Nature Reviews, 2004

Rational Drug Discovery "Pipeline" ...
... a myth?

COMMENTARY

DRUG DEVELOPMENT

An End to the Myth: There Is No Drug Development Pipeline

Kristin Baxter,[1,2] Elizabeth Horn,[1] Neely Gal-Edd,[1] Kristi Zonno,[1,3] James O'Leary,[1] Patrick F. Terry,[4] Sharon F. Terry[1]*

A new map is presented for creating an open, collaborative, and coordinated system for drug development.

THE CURRENT MODEL IS DEFUNCT

There is abundant evidence that the current drug development system is inadequate, unsustainable, and failing those who need it

tists and administrators in surveys, salons, and structured interviews. As a result of this information gathering, we propose a new model for depicting the drug development

igating the Ecosystem of Translational Sciences (NETS) (Fig. 1). This model is not the only possible model of drug development but is offered as a representation that reflects a culture of openness and transparency, seeks to alleviate misaligned incentives, acknowledges the nuances of the process, and provides a map for creating an open, collaborative, and coordinated system for drug development in the 21st century.

NETWORK APPROACH

The NETS model of drug development provides a systems and network perspective that transcends a focus on traditional components. Systems thinking requires that drug development be viewed as parts

nies, (ii) the U.S. and European government agencies, (iii) health-care payers, (iv) patient advocacy groups, and (v) academic scien-

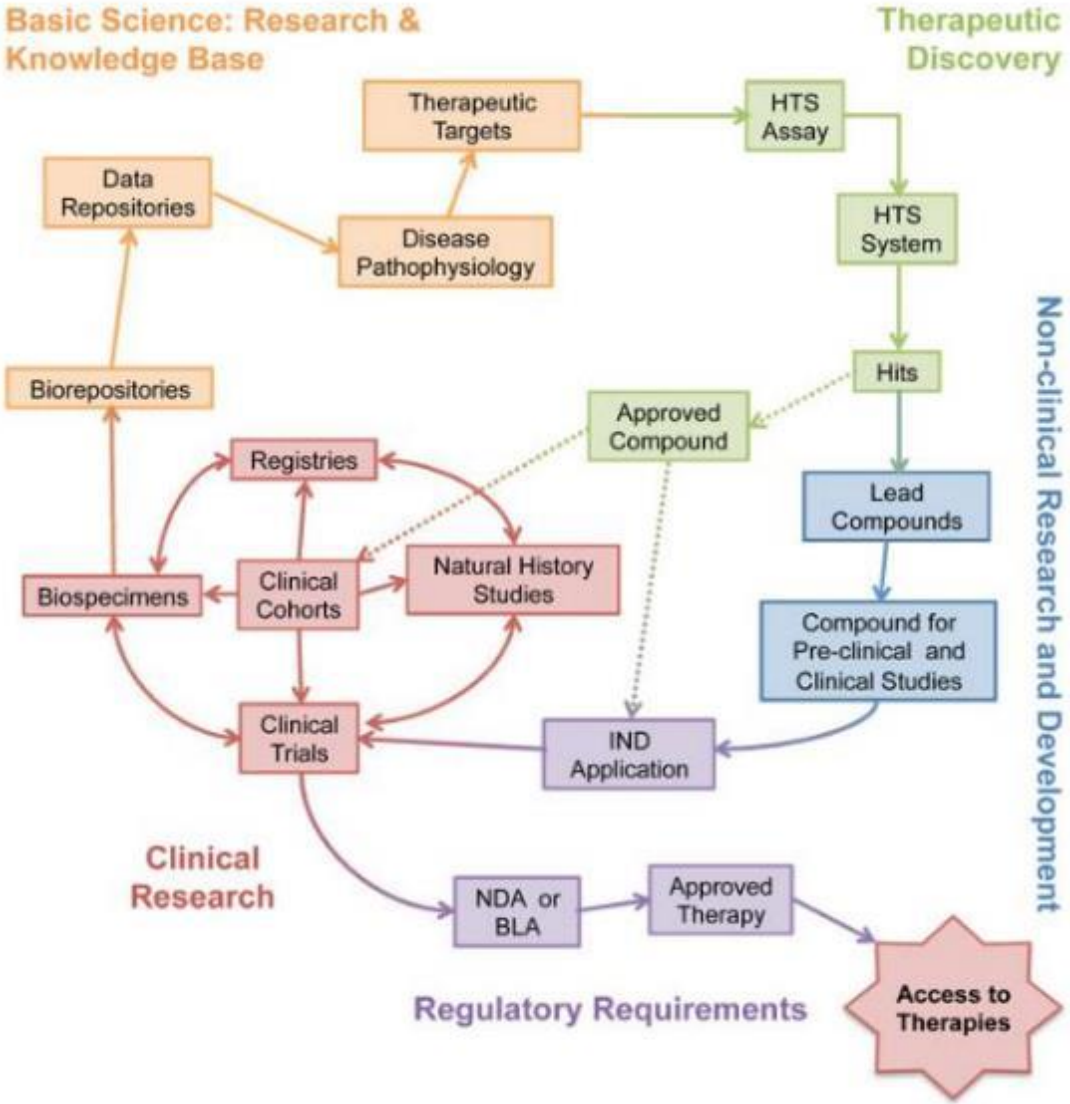
[1]Genetic Alliance, Washington, DC 20008, USA. [2]Booz Allen Hamilton, McLean, VA 22102, USA. [3]Myriad Genetics, Salt Lake City, Utah 84108, USA. [4]PXE International, Washington, DC 20008, USA.
*Corresponding author. E-mail: sterry@geneticalliance.org

scientists; clinical services; policy, regulatory, and reimbursement specialists; and consumers, patients, and advocates. These teams require a model that is sufficiently complex but allows these normally disparate players to assemble.

To illustrate these observations, we created a networked systems model called Nav-

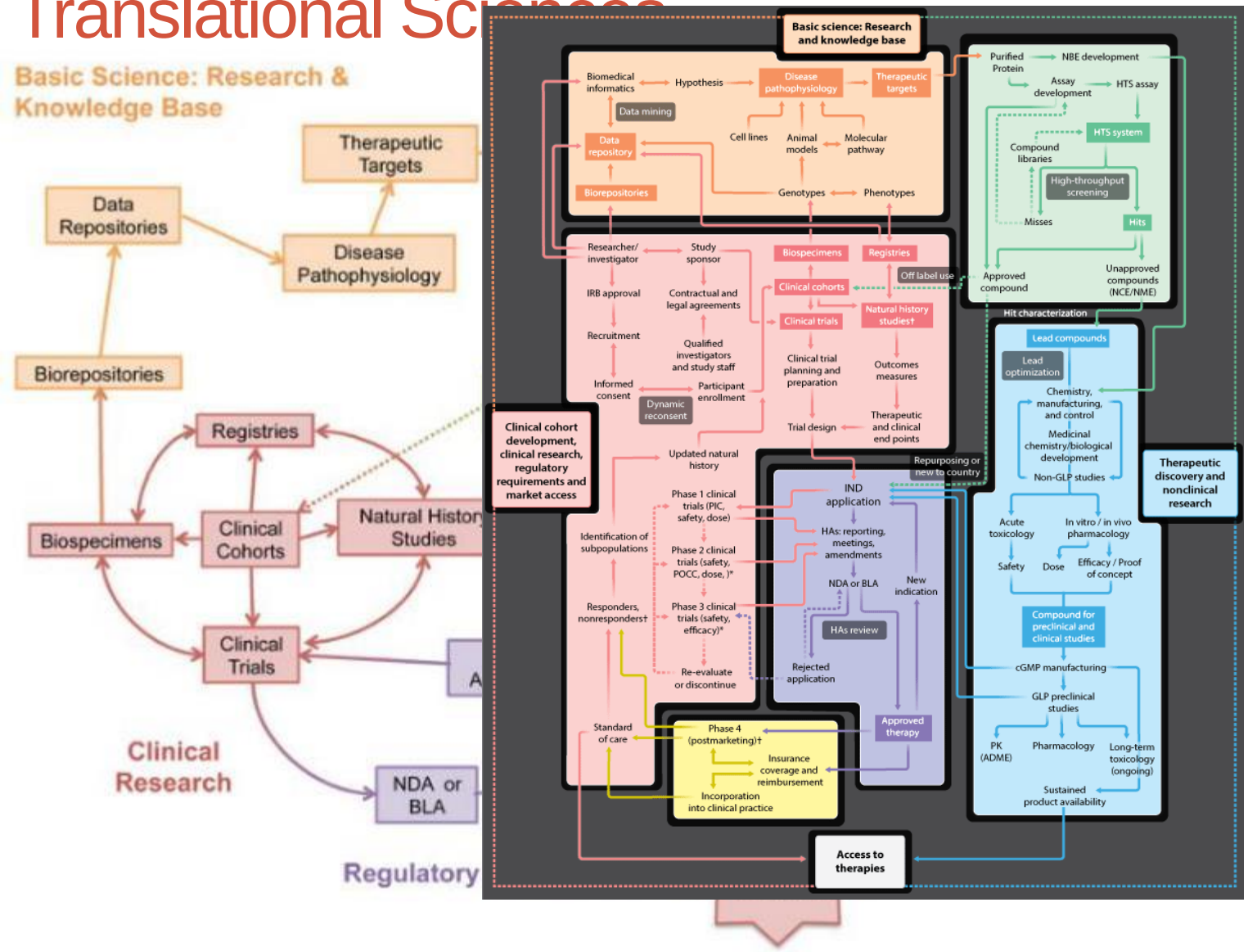
holder collaborations. Unlike the traditional model in which rigid boundaries discourage stakeholder interactions, each of the interfaces between the various "neighborhoods" [highlighted in different colors on the map (Fig. 1)] presents an opportunity for stakeholders to work together in a dynamic network. As an example, patient registries and

Navigating the Ecosystem of Translational Sciences



http://www.geneticalliance.org/programs/biotrust/nets

Navigating the Ecosystem of Translational Sciences



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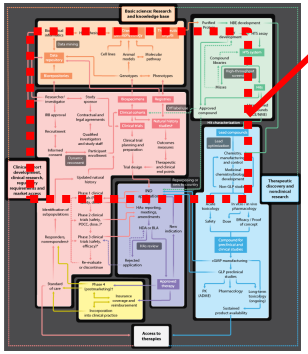
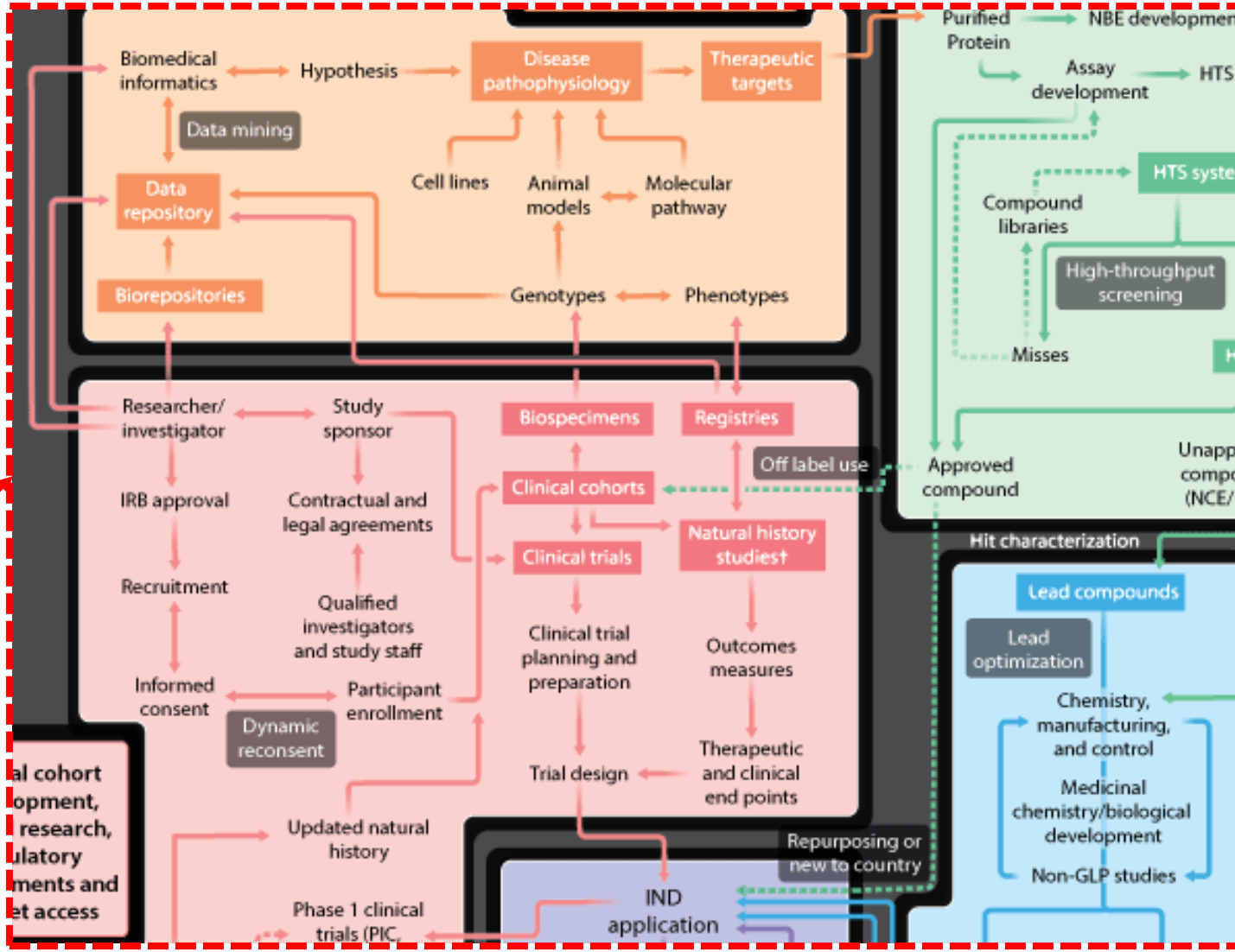
Navigating the Ecosystem of Translational Sciences

Collaboration and feedback loops among: clinical and non-clinical research, basic science and **data science**





Drug Discovery Paradigms: Take home messages

- Historically, finding new medicines was empirical (i.e. natural products, traditional medicine).
- Science has produced “wonder drugs” such as antibiotics and vaccines. But "wonder drugs" do not exist for all conditions.
- Molecular biology has transformed drug discovery into a rational design process – when it works. Some great successes, but process may have “run out of steam”.
- The current rational drug discovery & development process is lengthy, expensive and risky.
- New integrative paradigm combines systems biology and data science.