

Frederick National Laboratory for Cancer Research



Accelerating Therapeutics for Opportunities in Medicine (ATOM) - Update

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Frederick National Laboratory Advisory Committee

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ATOM Update Overview

- **Defining ATOM**
 - An open consortium
 - A CRADA driven platform
 - An emerging public-private resource
- **Progress Updates**
 - Building capabilities
 - Building capacity
 - Building the community
- **Looking Ahead**
 - Technical developments
 - Expanding involvement
 - Meeting the challenge

Defining ATOM

An open, public-private consortium, launched with a CRADA, creating a national-scale pre-competitive resource to accelerate cancer drug development

Drug Discovery: Long, Costly & High Failure

Seeking a better way to get medicines to patients



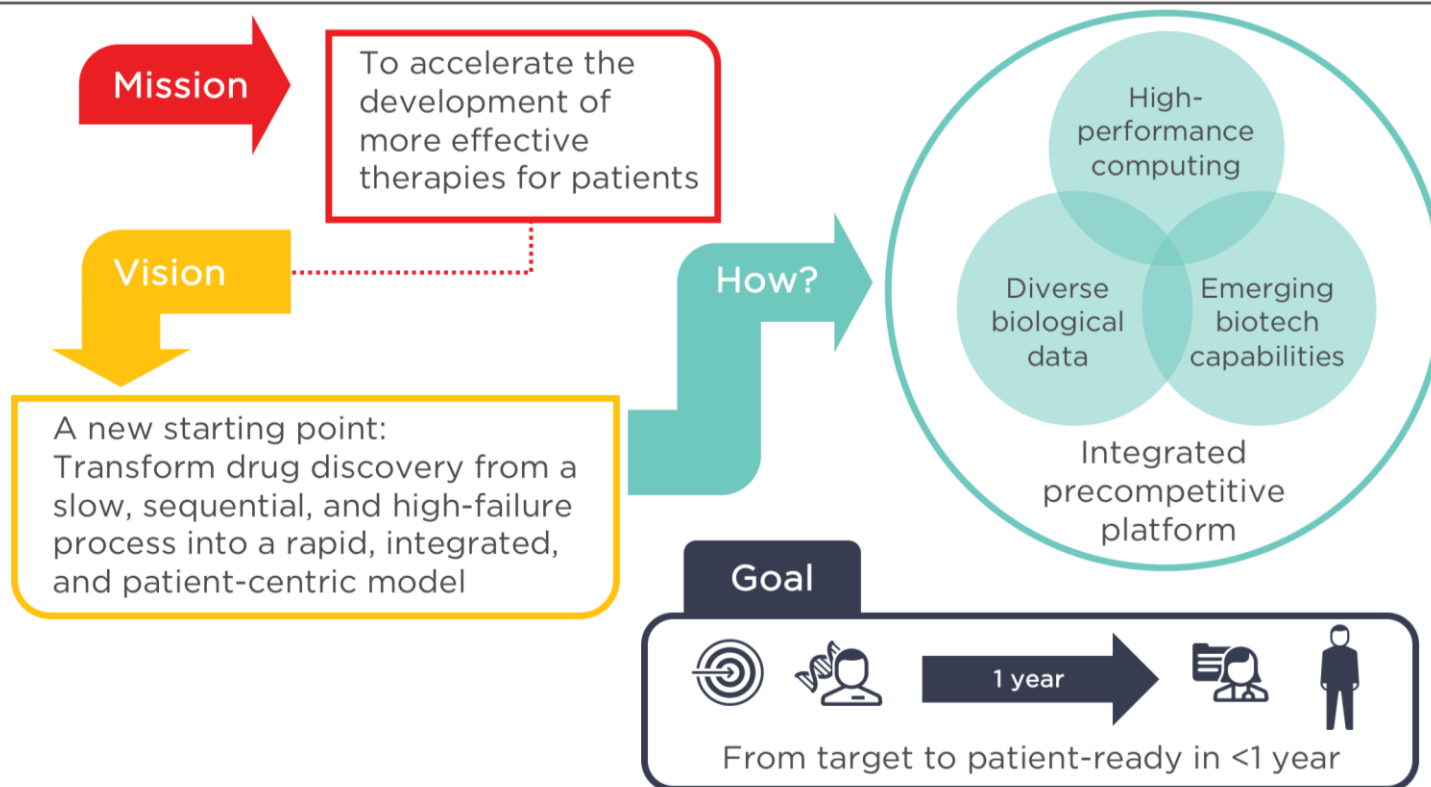
Preclinical issues:

- Average time: 5.5 years
- 33% of total cost of medicine development
- Millions of molecules tested, 1000s made, and most fail
- Clinical success rates still only 12%, indicating poor translation in patients

Source: <http://www.nature.com/nrd/journal/v9/n3/pdf/nrd3078.pdf>

Accelerating Therapeutics for Opportunities in Medicine

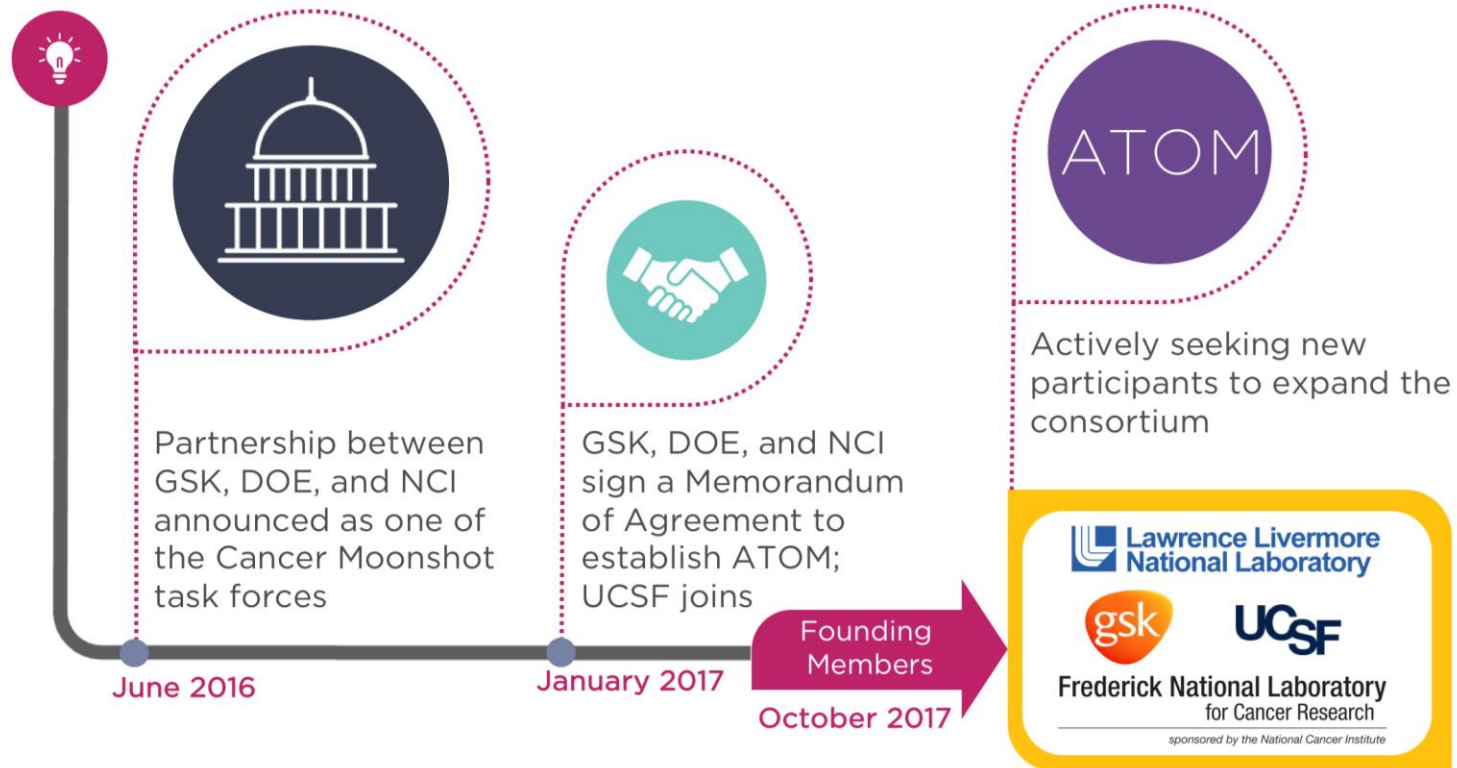
About ATOM



ATOM

Foundations for an Open ATOM Consortium

Establishing a public-private partnership

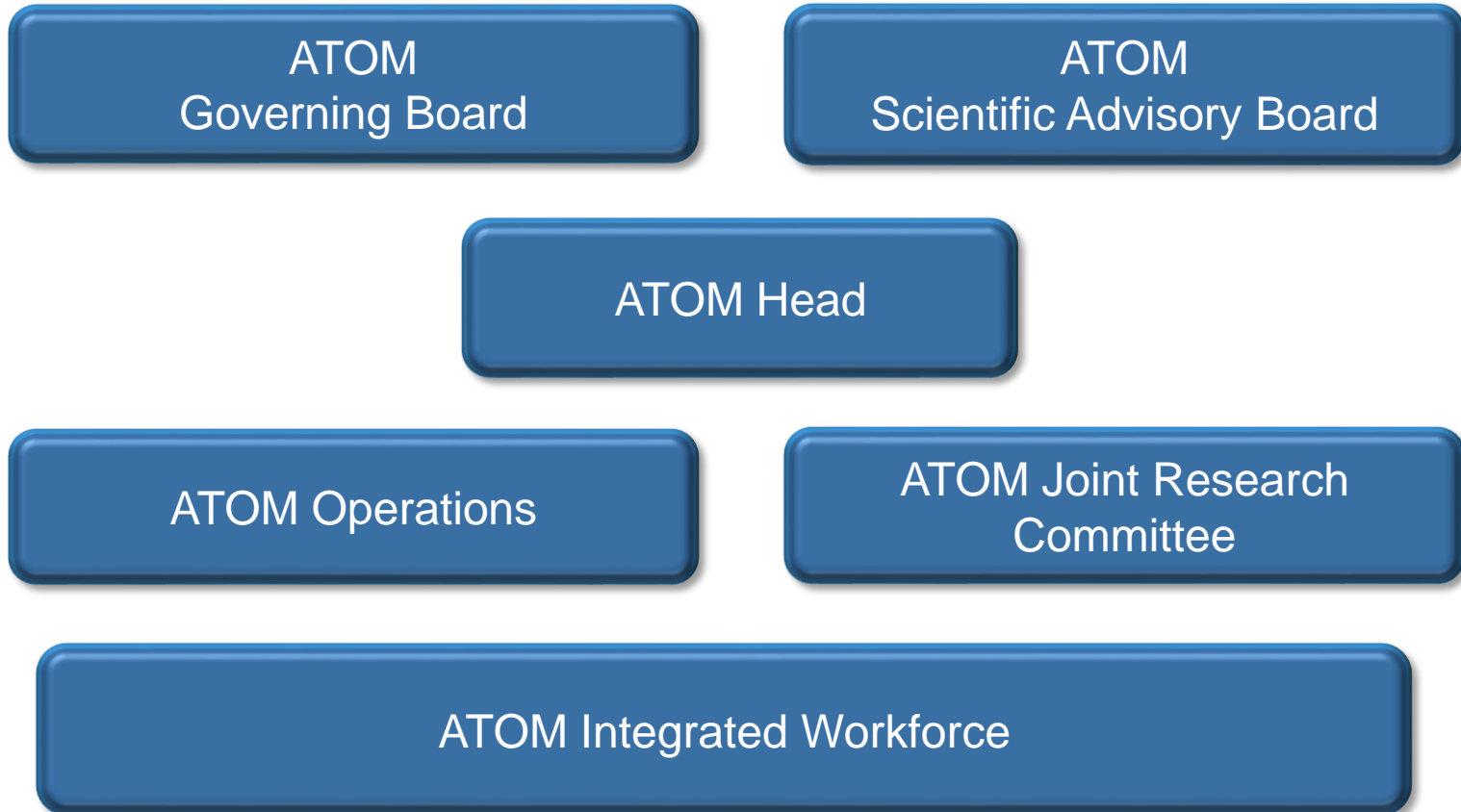


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ATOM Consortium and CRADA

- **ATOM Consortium**
 - Organizational framework for government, industry and academic collaboration
 - Collaborative, in the public-interest
 - Open to new members
 - Aligns to shared aims of NCI-DOE collaboration
- **ATOM Platform**
 - Launched with multi-year CRADA
 - Supporting active learning integration across experiment, data, simulation
 - Publicly accessible integrated platform
 - Publicly accessible models to accelerate drug development
 - Evolving

ATOM Organizational Structure



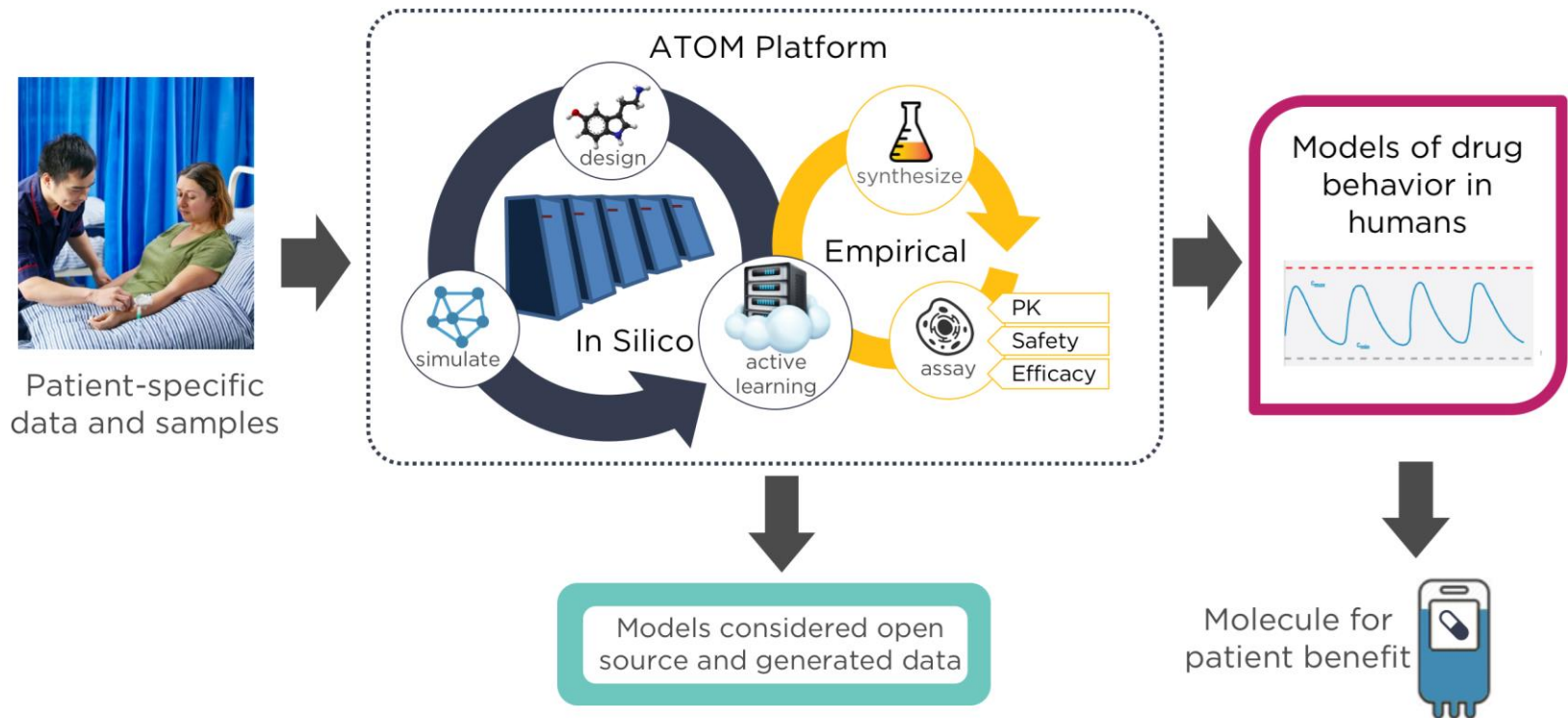
ATOM Organizational Updates

- **ATOM Governing Board**
 - Organizational leads from each consortium members in place
 - Regular meetings established – including member site rotation
- **ATOM Scientific Advisory Board**
 - In development
- **ATOM Head**
 - Interim leadership from on-site senior personnel
- **ATOM Joint Research Committee**
 - In place with scientific leads from each organization
 - Delivered ATOM technical research plan
- **ATOM Operations**
 - Supporting ATOM outreach, legal, procurement, personnel across collaborating organizations

- **Frederick National Laboratory**
 - **ATOM Governing Board**
 - Ethan Dmitrovsky, Eric Stahlberg
 - **ATOM Joint Research Committee**
 - Dwight Nissley
 - **ATOM Operations**
 - Deb Hope (lead)
 - Andrew Quong, Vladimir Popov, Claudia Haywood, Monica Slate, Frank Blanchard, Max Cole
- **NCI**
 - Program Lead - Emily Greenspan (CBIIT)
 - Outreach - Izumi Hinkson (CBIIT)

Accelerated Drug Discovery Concept

Vision of ATOM workflow in practice



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ATOM Integrated Platform – an Emerging Resource

From slow, sequential, & high-failure to rapid, integrated, and patient-centric

Computational prediction at the protein, cell, tumor, tissue, organ and organism level



Rapid empirical testing is focused on validating and optimizing computational predictions



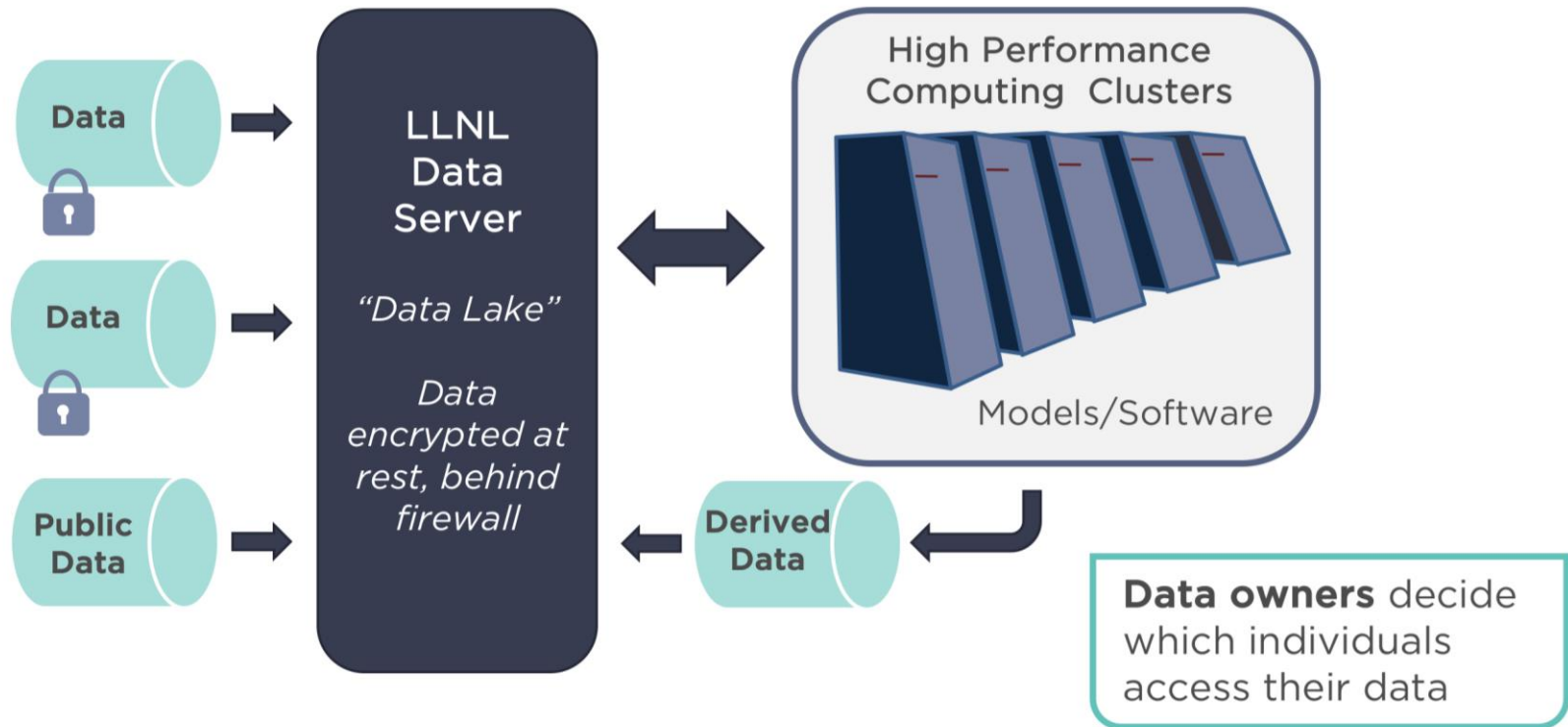
In silico and complex in vitro models reduce reliance on non-human models



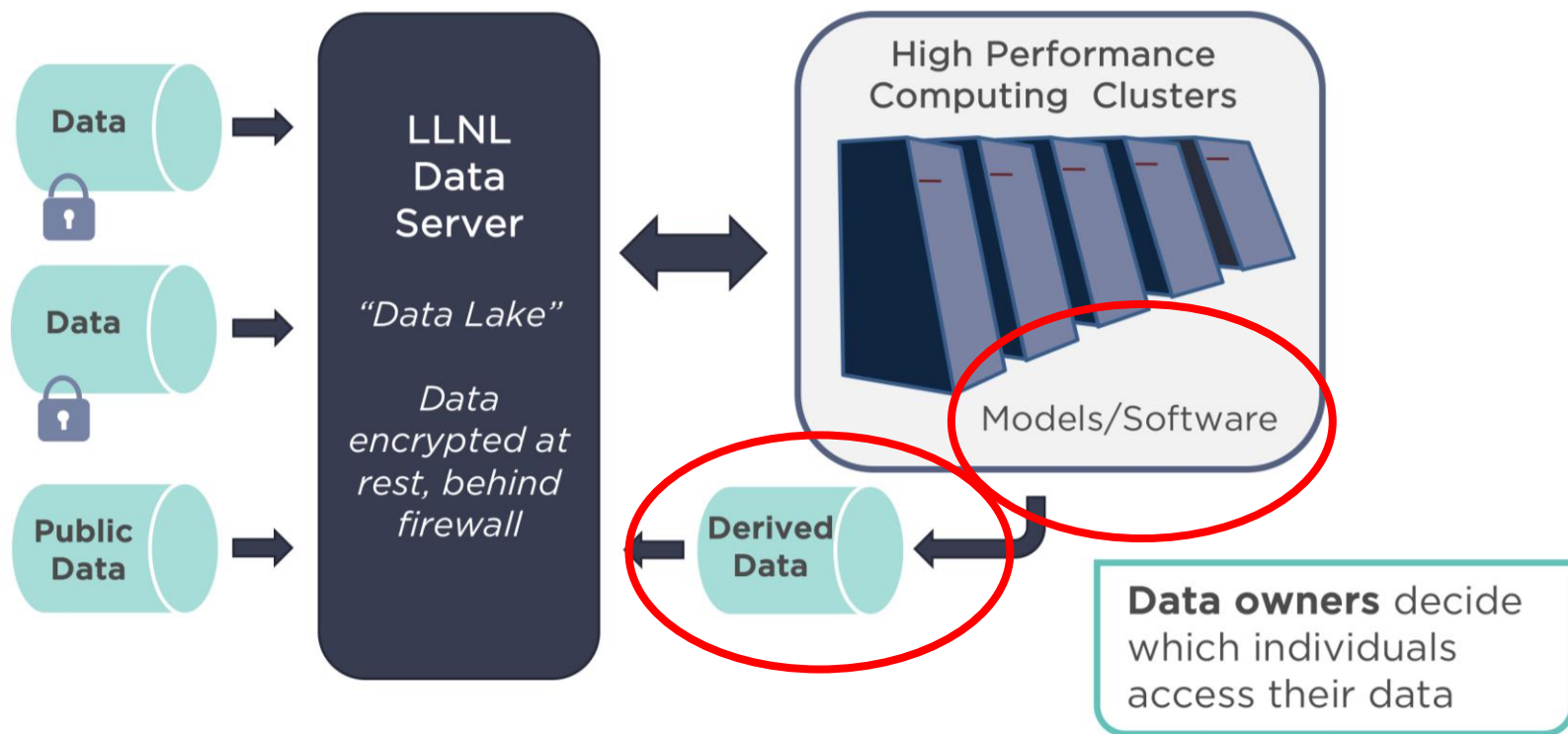
Regulatory requirements supported by in vitro data and in silico predictions



National Resource Level Data, Compute and Security



National Resource Level Data, Compute and Security



ATOM pre-competitive platform delivers models, software and derived data

Progress Updates

Building organizational, data, and technical capabilities with capacity and opportunities for the community

Initial ATOM Accomplishments

Since founding in October 2017



Space founded in
San Francisco



Staffed with 28
People from 4
Organizations



Governing Board, Site
Head and Teams in
Place

• Stage 1 R&D Activities Began in Feb 2018

- **Data:**
 - Policy and infrastructure established
 - ingested private and public datasets
 - Analyzed diversity and identified gaps for parameters of current interest
- **PK:** 13 different data-driven solubility models have been built and tested using new and existing data sets.
- **Safety:** Data-driven models built for 84 common liability assays with 3 featurization methods.
- **Mechanistic modeling:**
 - computed features for ~ 2M compounds
 - built and optimized atomistic protein models for 57 liability targets for use in heart and liver toxicity predictions.

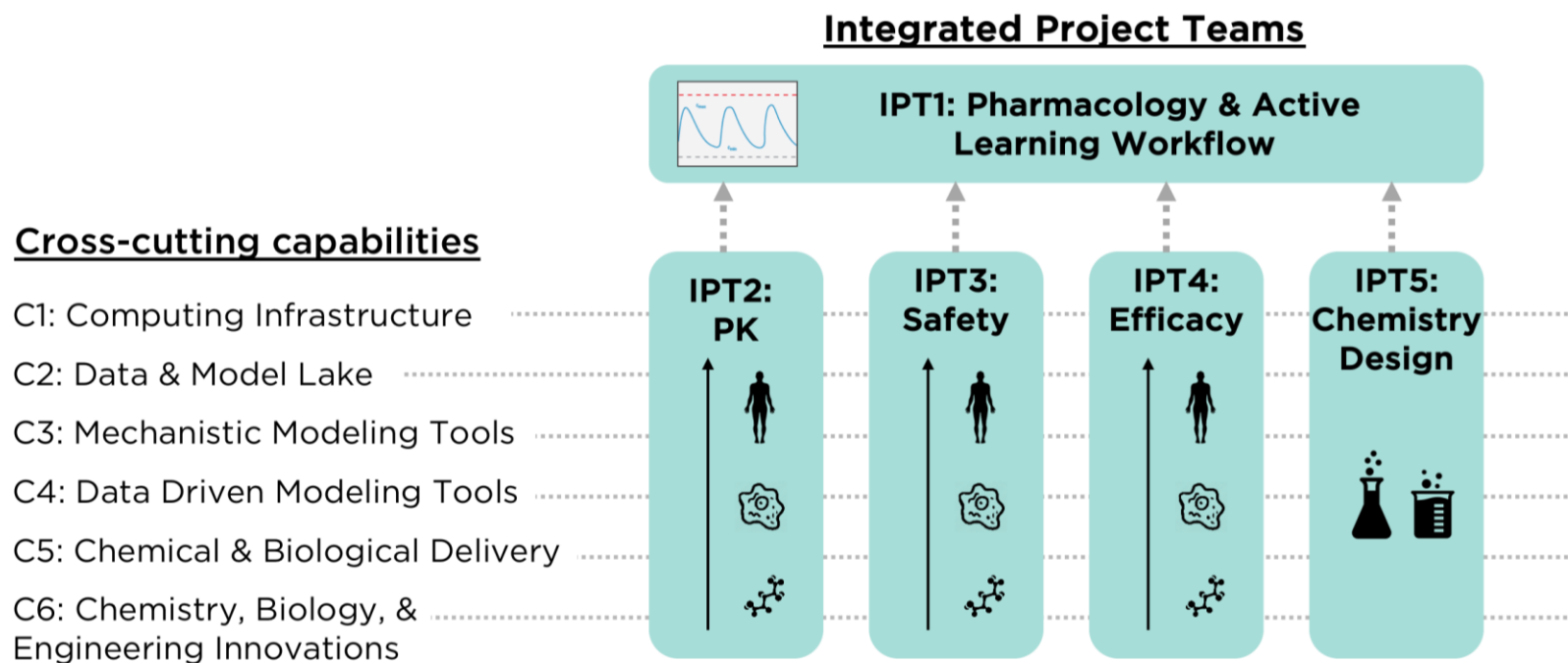
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What is Different about ATOM's Approach?

Integration

- **Integration** of predictions of compound properties across PK, safety, and efficacy
- **Integration** of computational and experimental capabilities in an active-learning based approach
- **Integration** and acceleration of chemical synthesis and experimental data collection to facilitate the active-learning process
- **Integration** of machine learning and mechanistic models to create hybrid models for compound activity predictions
- **Integration** of partners to create the ecosystem

Matrix approach integrating experiment and computation



ATOM Workforce



- **FNL ATOM Operations Lead – Deb Hope**
- **FNL ATOM Fellows**
 - Initial fellows supported by NCI Center for Biomedical Informatics and Information Technology (CBIIT)
 - Opportunities for fellows to bridge public, private and academic communities
 - Foundation for future collaborative workforce
 - First ATOM fellow on-board, Second arriving in July
- **FNL ATOM Data Scientist on-site**
 - In process
- **Part of 28 integrated personnel working jointly on ATOM efforts**

Initial Data Assets : GSK's proprietary data

ATOM has access to data from approximately 2 million compounds

Source	# Compounds	Specific Data Insights
Post-candidate selection programs no longer of interest to GSK	500 (2700 with variants)	<ul style="list-style-type: none"> In vitro and in vivo results (see below) ~100 compounds with anonymized human clinical data
Unique compounds synthesized in lead optimization over last 17 years	515 k	<ul style="list-style-type: none"> Structure-activity relationships with learnings on protein target pocket
Retired High Throughput Screening (HTS) compounds	1 M	<ul style="list-style-type: none"> in vitro assays against diverse protein targets and physicochemical properties
Commercially available compounds in current HTS collection	420K	<ul style="list-style-type: none"> in vitro assay data gained over the past ten years for a diversity of protein targets

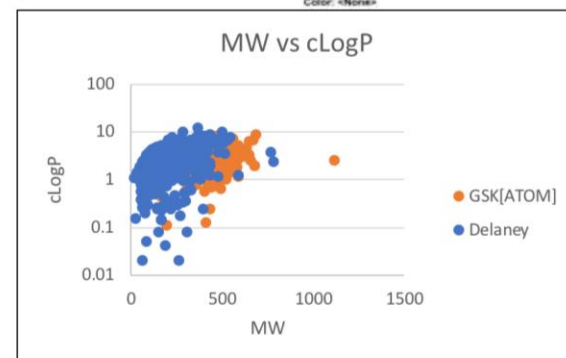
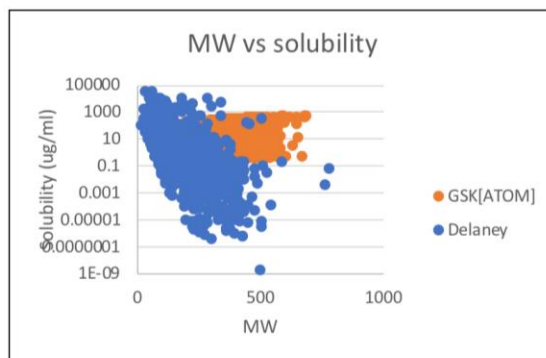
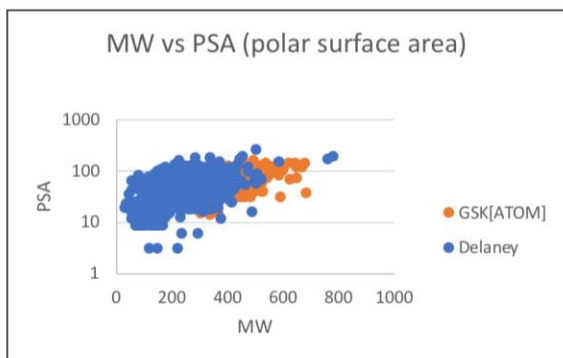
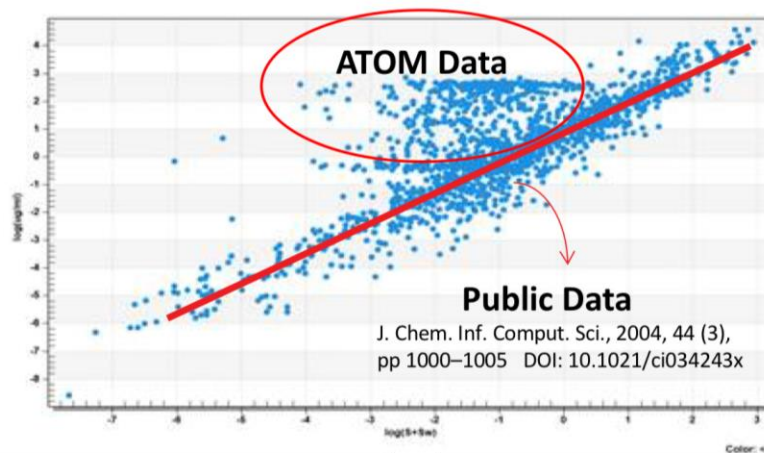
Above data sets include, as available:

- in vitro enzyme and cell-based assay screening data against
- physicochemical experimental and calculated properties
- ex vivo ADME data
- in vivo pharmacokinetic, toxicokinetic, and animal safety data
- protein ligand crystal structures

Value of Data Diversity – Solubility Models

Models built only on public data perform poorly when predicting drug like molecules from the GSK data set.

Largely due to MW and Physical property differences.



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ATOM Outreach Efforts



ATOM@AACR Outreach Effort

Emails sent to:

515 pharma contacts from FNL and UCSF Strategic Alliances

69 Cancer center directors

50 NCI academic collaborators

6 national labs directly invited (ANL, ORNL, PNNL, BNL, LANL, and Sandia)

Additional invites circulated through DOE HQ to DOE system-wide users

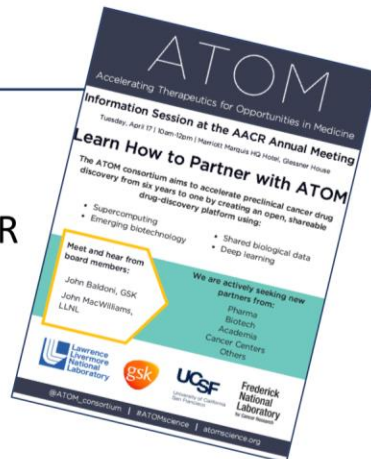
Online presence across multiple websites and platforms:

- FNL website
- ATOM website
- ATOM LinkedIn
- Personal LinkedIn accounts
- FNL, FNL PDO, ATOM, and NCI NCIP Twitter accounts
- FNL Facebook account



400

flyers circulated at AACR (NCI booth, ATOM event, and meet the experts meetings)



Social media activity from FNL and FNL PDO:

20 Twitter posts:

- **11,836** views
- **141** engagements (clicks, retweets, likes)

3 Facebook posts:

- **481** people reached

ATOM is Moving Ahead

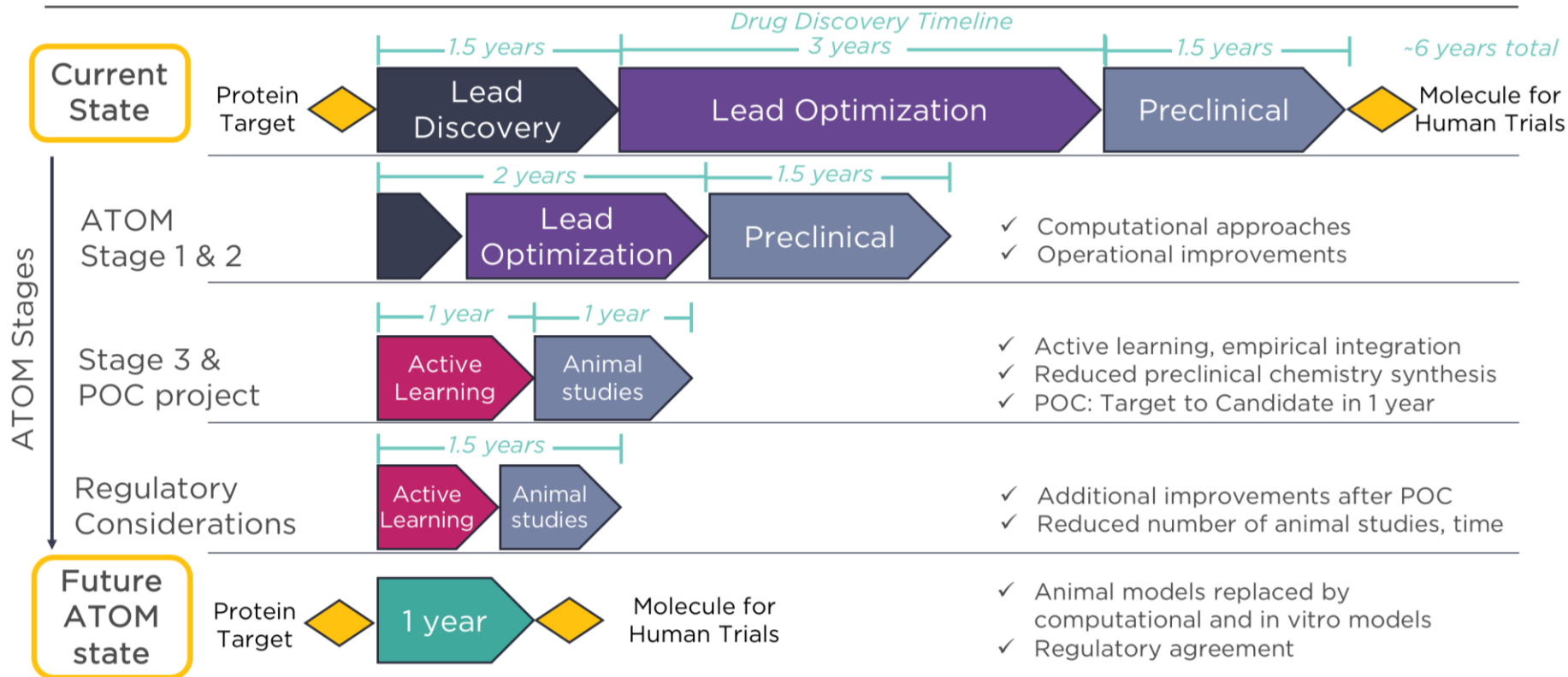
- First stage research underway with available data
- Staff on-site
- Integrated cross-discipline and cross-organizational environment
- Initial research plan
- Available data leading to insights in data and models
- Expanded involvement is key to success
- Outreach to new members underway

Looking Ahead

Broader participation, increasing data, and growing capabilities to meet the ATOM challenge

ATOM Roadmap

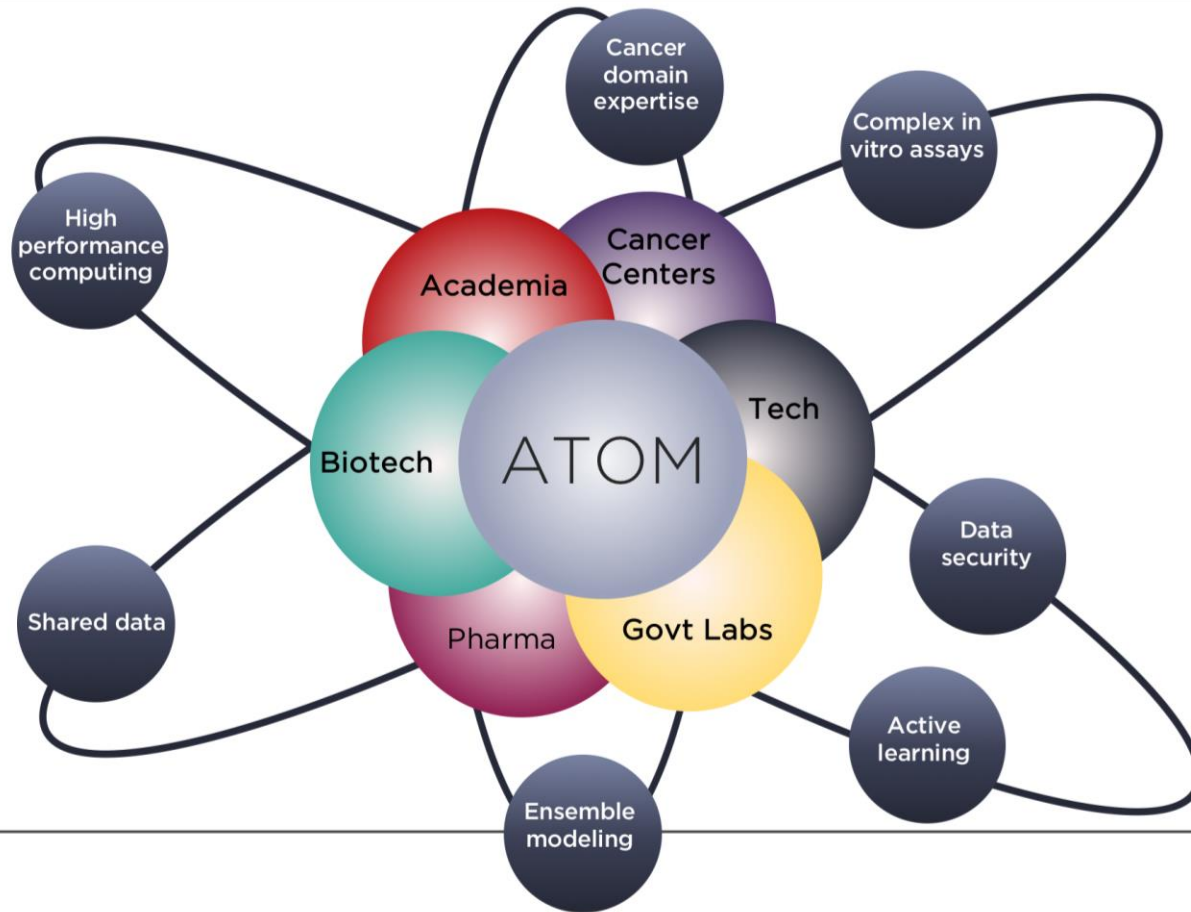
Multi-year strategy to reduce drug discovery timelines and costs



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The Consortium Approach

Why none of us can do this alone...



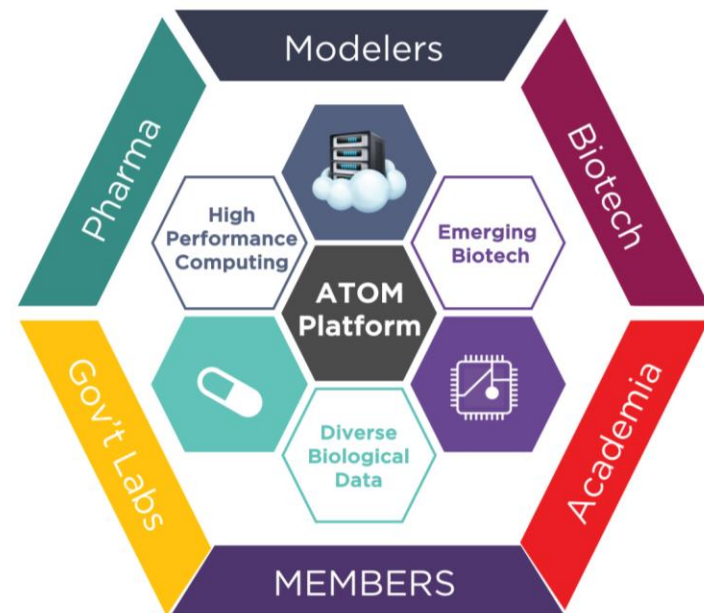
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ATOM Succeeds with the Community

Members contribute to & have access to unique pre-competitive platforms and algorithms.

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Ahead for Frederick National Laboratory

- Growing the ATOM community
- Expanding data resources
- Bringing forward additional expertise
- Developing new opportunities
- Delivering the ATOM resource

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Questions and Discussion

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