



OPCW

Organisation for the Prohibition of Chemical Weapons

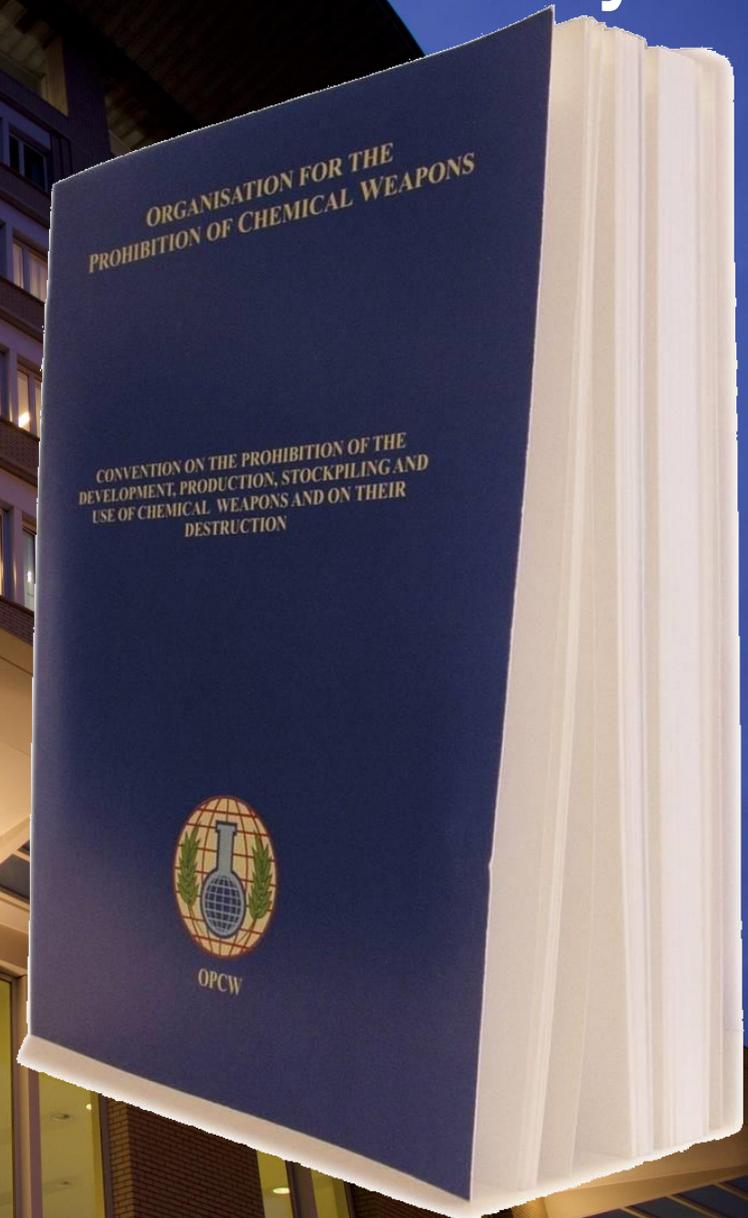
Barriers and Opportunities: Science, Technology, Disarmament and Non-proliferation

*2nd Annual Global Forum on Scientific Advances Important to the
Biological and Toxins Weapons Convention
Palais de Nations, Geneva, Switzerland
2 December 2019*

Jonathan E. Forman, Ph.D.

Science Policy Adviser and Secretary to the Scientific Advisory Board

Where Does Science Fit Into An International Disarmament and Non-Proliferation Treaty?



Where
Disarm

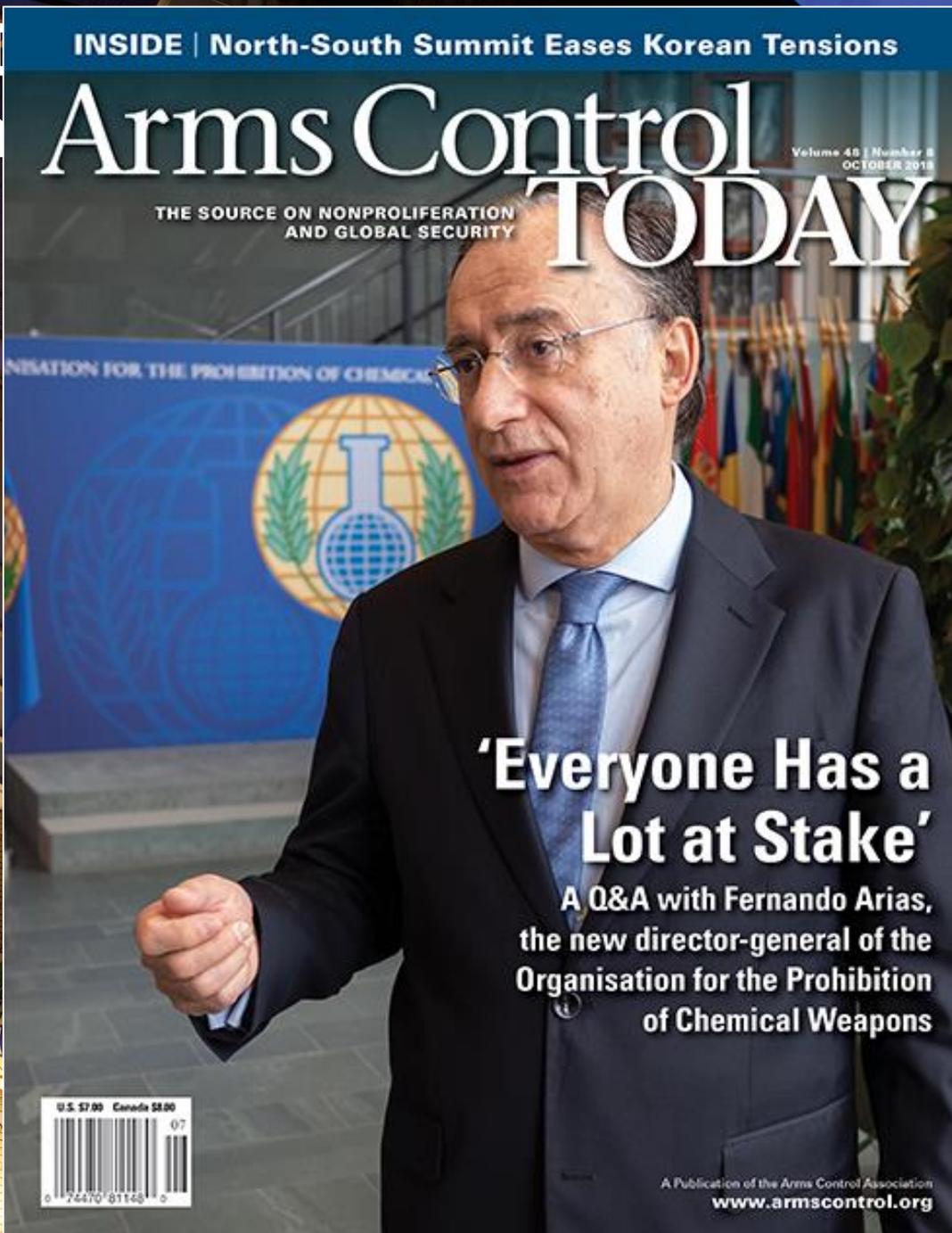
INSIDE | North-South Summit Eases Korean Tensions

Arms Control TODAY

Volume 48 | Number 8
OCTOBER 2018

THE SOURCE ON NONPROLIFERATION
AND GLOBAL SECURITY

ORGANISATION FOR THE PROHIBITION OF CHEMICAL WEAPONS



'Everyone Has a Lot at Stake'
A Q&A with Fernando Arias,
the new director-general of the
Organisation for the Prohibition
of Chemical Weapons

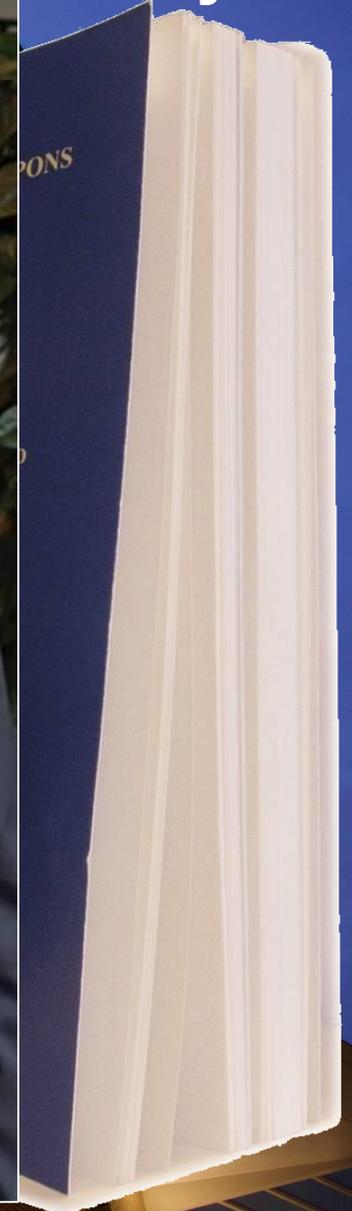
U.S. \$7.00 Canada \$8.00



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A Publication of the Arms Control Association
www.armscontrol.org

national
Treaty?



The Conventions Mandate the States Parties to Discuss Science

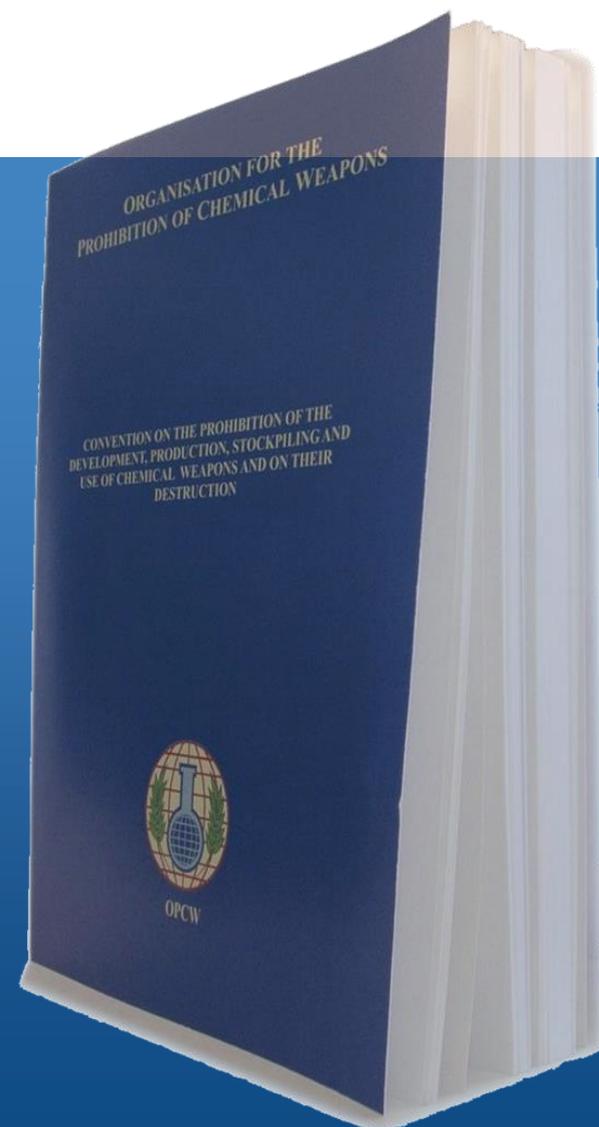
The Conference of States Parties Shall:

“Review scientific and technological developments that could affect the operation of this Convention and, in this context, direct the Director General to establish a Scientific Advisory Board to enable him, in the performance of his functions, to render specialized advice in areas of science and technology relevant to this Convention, to the Conference, the Executive Council or States Parties.”

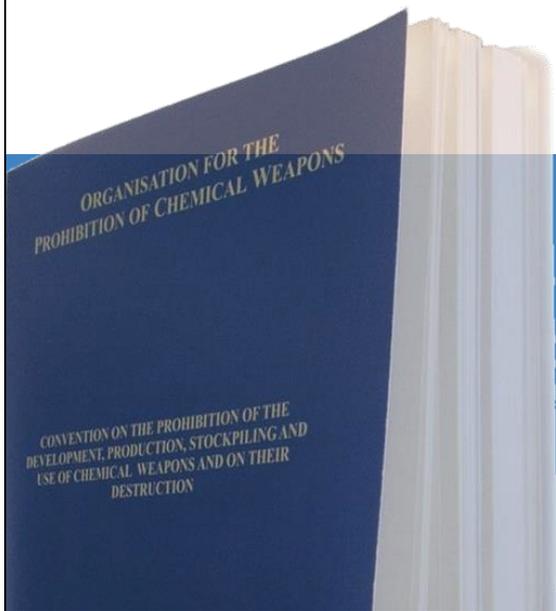
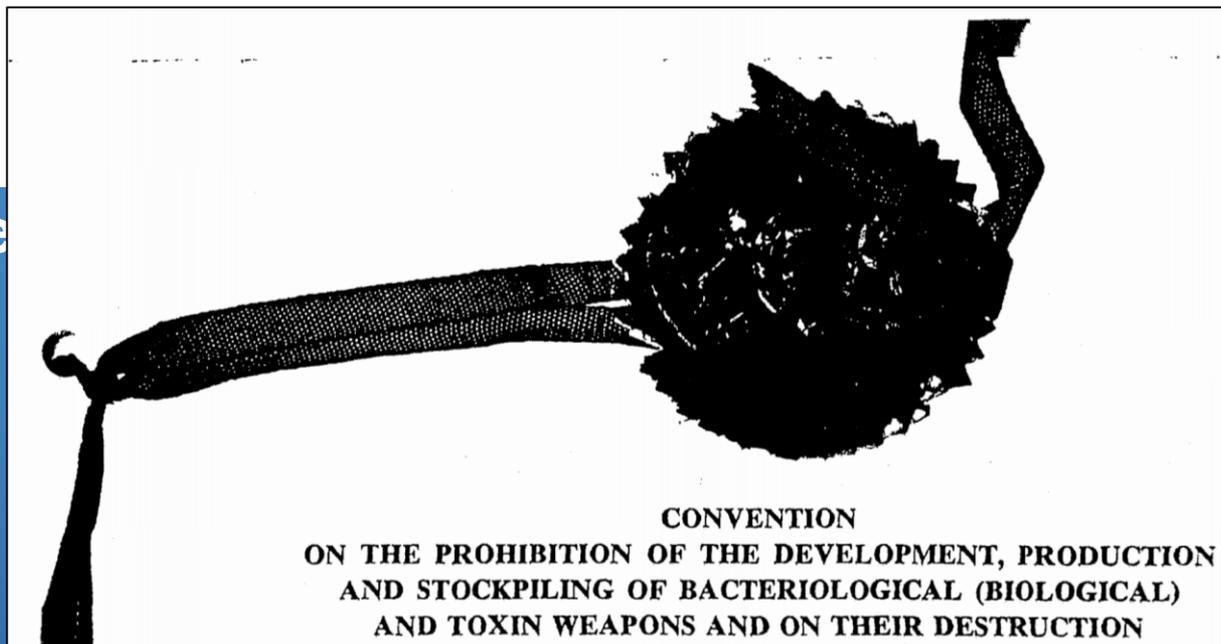
CWC Article VIII, Section B, paragraph 21(h)



OPCW



The Conventions Mandate the States Parties to Discuss Science



The

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Conference, t
Parties.”

ARTICLE XII

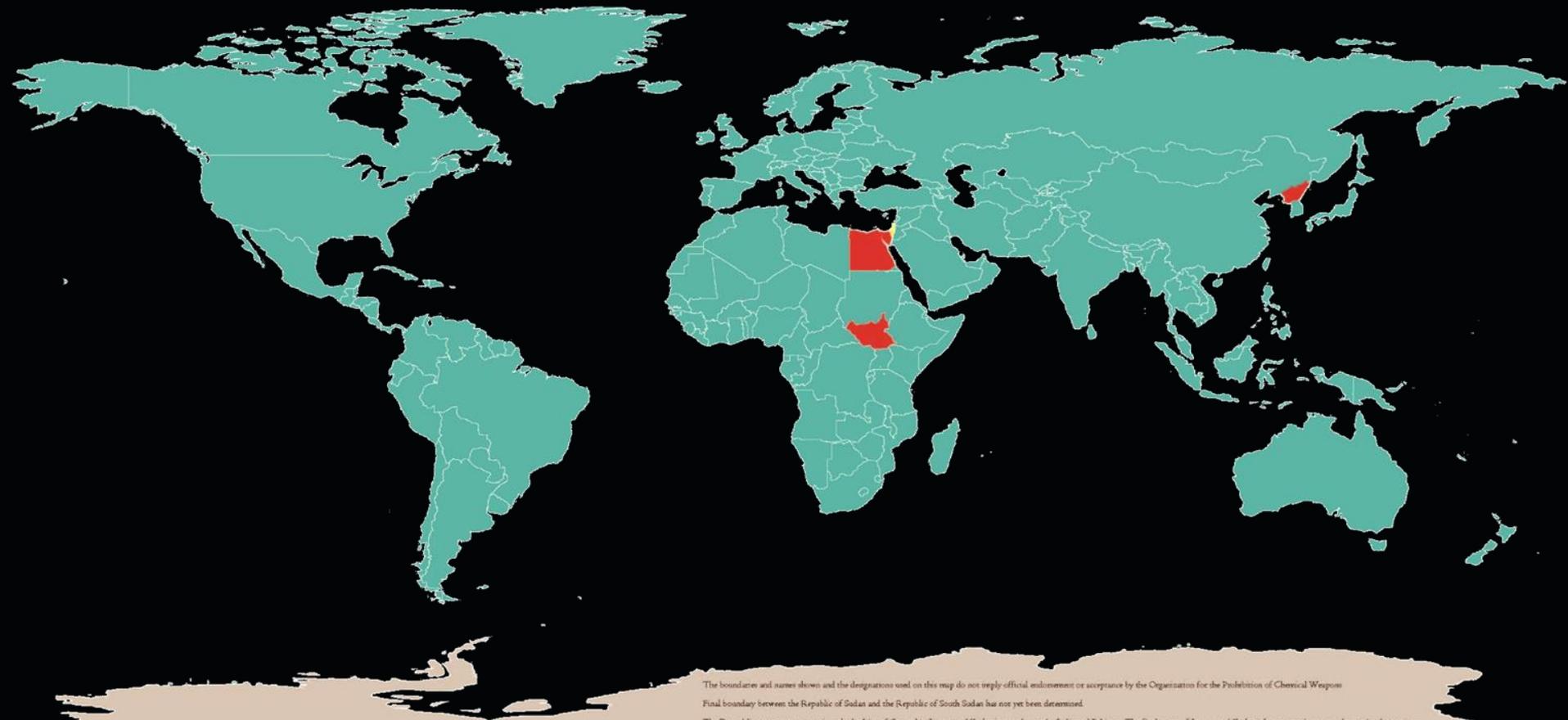
Five years after the entry into force of this Convention, or earlier if it is requested by a majority of Parties to the Convention by submitting a proposal to this effect to the Depositary Governments, a conference of States Parties to the Convention shall be held at Geneva, Switzerland, to review the operation of the Convention, with a view to assuring that the purposes of the preamble and the provisions of the Convention, including the provisions concerning negotiations on chemical weapons, are being realised. Such review shall take into account any new scientific and technological developments relevant to the Convention.

CWC Article VIII,



OPCW

How Do 193 “States Parties” Discuss Science?



Signed Without Ratification

Non-Signatory

How Do 193 “States Parties” Discuss Science?



Signed Without Ratification

Non-Signatory

How Do 193 “States Parties” Discuss Science?



The boundaries and names shown and the designations used on this map do not imply official endorsement or acceptance by the Organization for the Prohibition of Chemical Weapons.
Final boundary between the Republic of Sudan and the Republic of South Sudan has not yet been determined.

Signed Without Ratification

Non-Signatory

How Do 193 “States Parties” Discuss Science?



Is it any clearer amongst the 183
States Parties to the BTWC?

The boundaries and names shown and the designations used on this map do not imply official endorsement or acceptance by the Organization for the Prohibition of Chemical Weapons.
Final boundary between the Republic of Sudan and the Republic of South Sudan has not yet been determined.

Signed Without Ratification

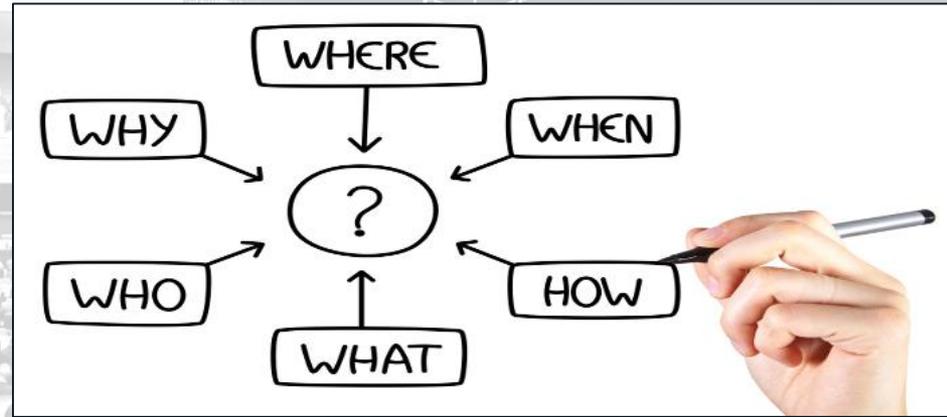
Non-Signatory

Can the Science Connect to Policy Priorities?



- **Science:** discovery, evidence, knowledge (running experiments)

- **Policy:** values and norms (defining outcomes)

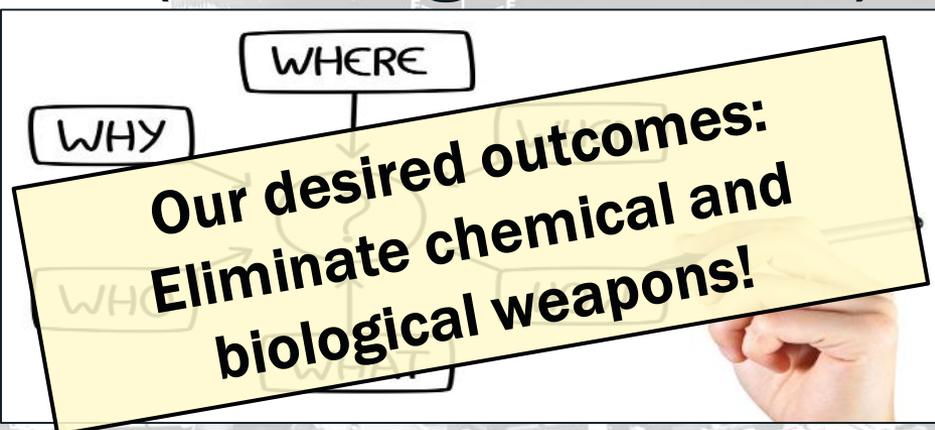


Can the Science Connect to Policy Priorities?



- **Science:** discovery, evidence, knowledge (running experiments)

- **Policy:** values and norms (defining outcomes)





THE BOOK OF
**TOTALLY
IRRESPONSIBLE
SCIENCE**

FEATURING

- ★ How to Grow a Frankenstein Hand!
- ★ How to Turn Milk into Stone!
- ★ How to Make a Potato Gun!



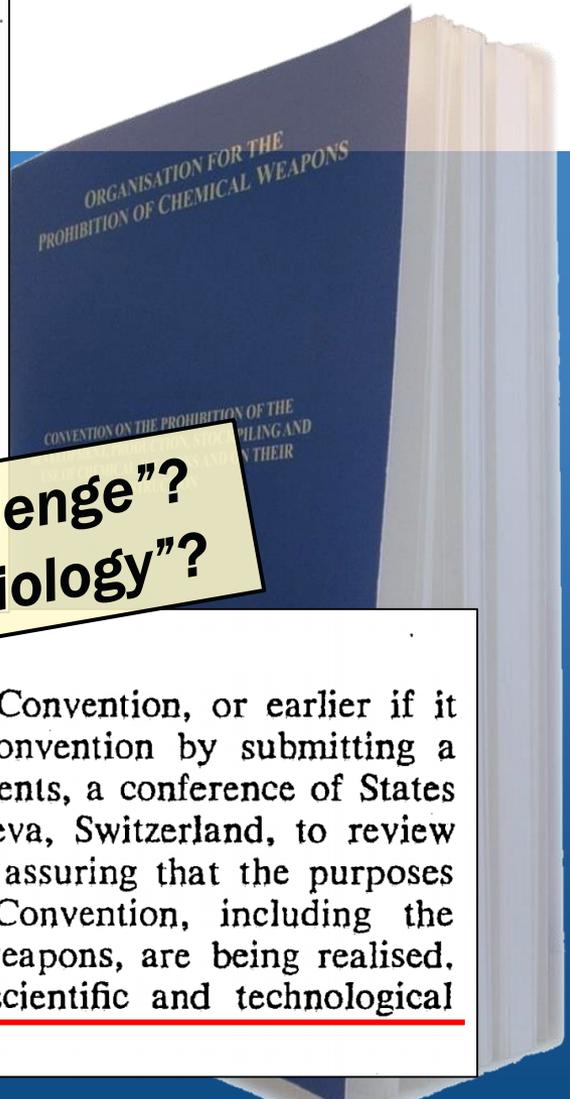
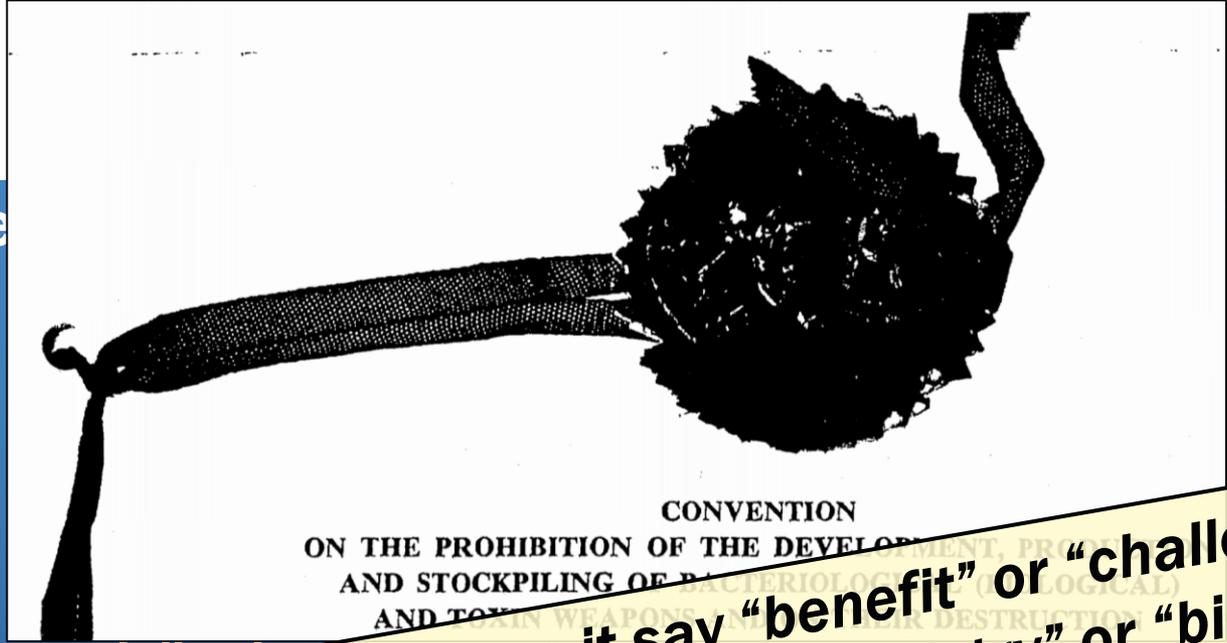
PLUS

- ★ Cola Geysers!
- ★ Burning Ice!
- ★ DIY Blubber!
- ★ Homemade Lightning!
- ★ And More ...



**64 DARING
EXPERIMENTS**

The Conventions Mandate the States Parties to Discuss Science



Where does it say “benefit” or “challenge”?
Where does it say “chemistry” or “biology”?

specialized
technol
Confere
Parties.”

entry into force of this Convention, or earlier if it is requested by a majority of Parties to the Convention by submitting a proposal to this effect to the Depository Governments, a conference of States Parties to the Convention shall be held at Geneva, Switzerland, to review the operation of the Convention, with a view to assuring that the purposes of the preamble and the provisions of the Convention, including the provisions concerning negotiations on chemical weapons, are being realised. Such review shall take into account any new scientific and technological developments relevant to the Convention.

CWC Article VIII,



OPCW

Treaty Implementation

“The Convention”

```
graph TD; A["The Convention"] --- B["Disarmament (Destruction and Verification)"]; A --- C["Non-proliferation (Verification)"]; A --- D["Assistance and Protection against CWs"]; A --- E["International Cooperation"];
```

**Disarmament
(Destruction and
Verification)**

**Non-proliferation
(Verification)**

**Assistance and
Protection against CWs**

**International
Cooperation**

Treaty Implementation

“The Convention”



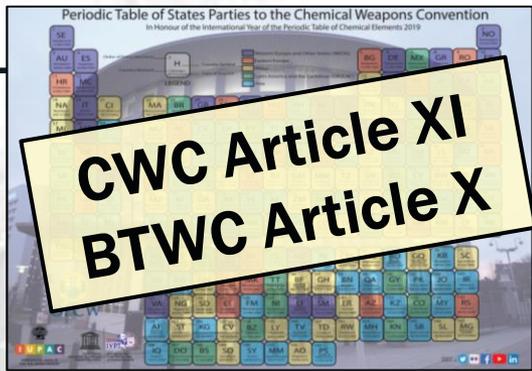
Periodic Table of States Parties to the Chemical Weapons Convention
In Honour of the International Year of the Periodic Table of Chemical Elements 2019

The table displays a grid of colored boxes, each representing a state party to the Chemical Weapons Convention. The boxes are color-coded by region: North America (purple), South America (green), Europe (blue), Africa (orange), Asia (red), and Oceania (yellow). The OICW logo is visible at the bottom left of the table.



Treaty Implementation

“The Convention”

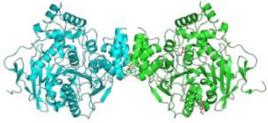


Without a Sound Scientific Basis There is No Treaty Implementation!

E. GLOSSARY

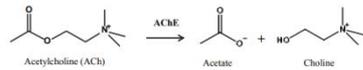
Acetylcholinesterase (AChE)

Acetylcholinesterase (AChE) is an enzyme [see also] responsible for breaking down the neurotransmitter acetylcholine (ACh) into choline and acetate. AChE is inhibited by the action of nerve agents [see also].



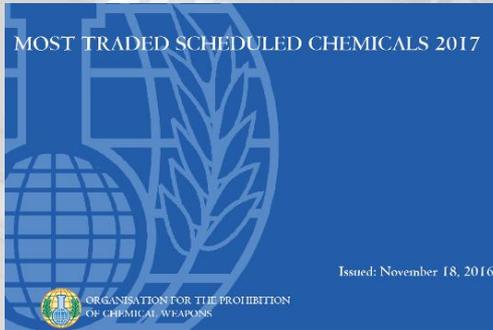
Crystal structure of the dimer of acetylcholinesterase (AChE) in complex with Xenon (Protein Data Bank 3M3D).²⁸

Break down of ACh to acetate and choline by AChE:



²⁸ Bohren, J., Brumstein, B., Tokor, L., Sömann, I., Sauman, J., Klebe, G. and Henke, A., Crystal structure of Acetylcholinesterase in complex with Xenon. RCSB Protein Data Bank, 2011, DOI: 10.2210/pdb/3M3D/pdb, www.rcsb.org/structure/3m3d

Glossary Version 1.0 - 27 May 2019



Article III



Articles IV and V



Article VI

Article II



Article VII



Article VIII



Articles IX and X



Article XI

Without a Sound Scientific Basis There is No Treaty Implementation!

E. GLOSSARY

Acetylcholinesterase (AChE)

Acetylcholinesterase (AChE) is an enzyme [see also] responsible for breaking down the neurotransmitter acetylcholine (ACh) into choline and acetate. AChE is inhibited by the action of nerve agents [see also].

MOST TRADED SCHEDULED CHEMICALS 2017



Article VII



Article VIII



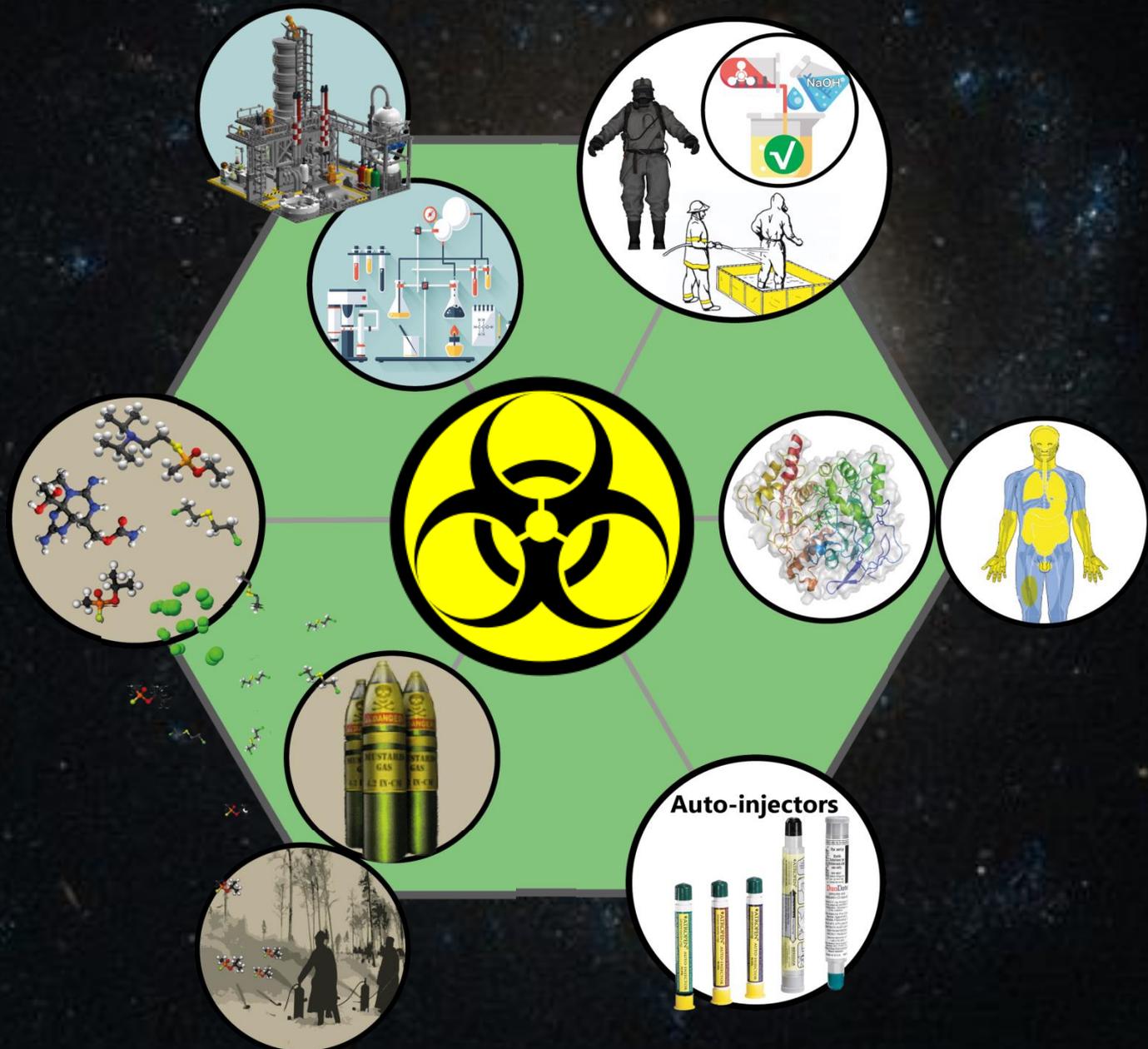
Articles IX and X

Article XI

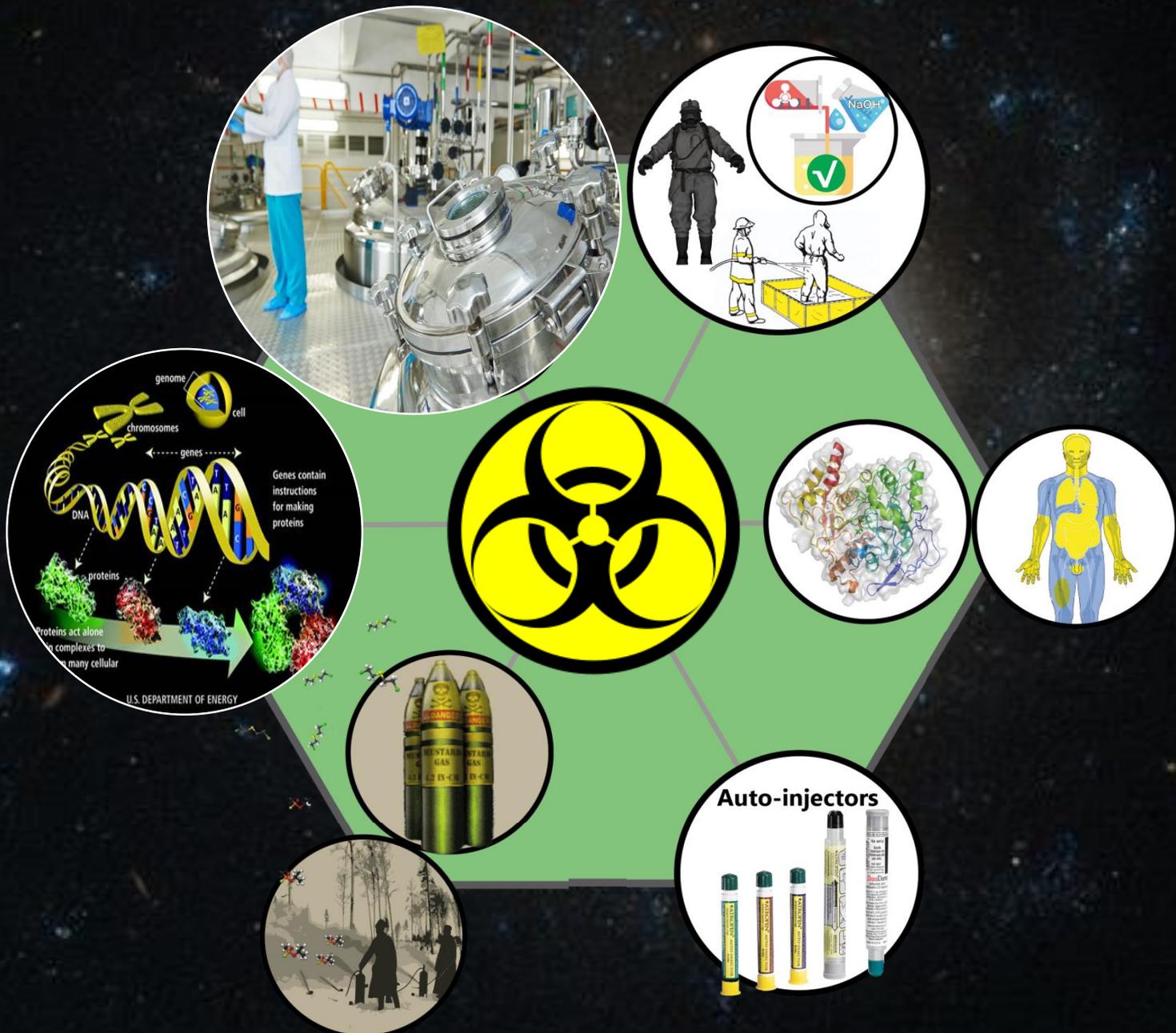


OPCW

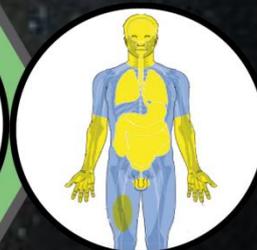
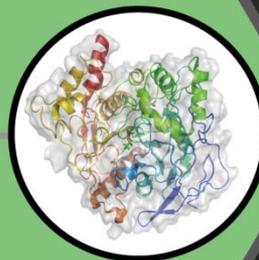
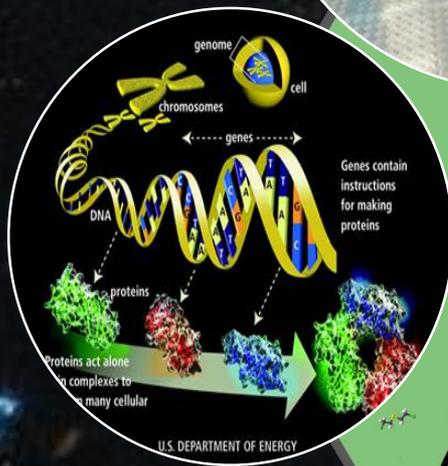
What Science Should be Our Priority?



What Science Should be Our Priority?



What Science Should be Our Priority?



Transdisciplinary and More Than (Bio)Chemicals

There is always more to the Story..

Muir et al. *Genome Biology* (2016) 17:53
DOI 10.1186/s13059-016-0917-0

Genome Biology

OPINION

Open Access



The real cost of sequencing: scaling computation to keep pace with data generation

Paul Muir^{1,2,3}, Shantao Li⁴, Shaoke Lou^{4,5}, Daifeng Wang^{4,5}, Daniel J Spakowicz^{4,5}, Leonidas Salichos^{4,5}, Jing Zhang^{4,5}, George M. Weinstock⁶, Farren Isaacs^{1,2}, Joel Rozowsky^{4,5} and Mark Gerstein^{4,5,7*}

Abstract

As the cost of sequencing continues to decrease and the amount of sequence data generated grows, new paradigms for data storage and analysis are increasingly important. The relative scaling behavior of these evolving technologies will impact genomics research moving forward.

organize high-throughput sequencing data. The SRA has grown significantly since its creation in 2007, and it now contains almost four petabytes (4×10^{15} bases), approximately half of which are open access [11]. These datasets present a challenge because they are too large for the old sharing and analysis paradigms, but recent innovations in computational technologies and approaches, especially the rise of cloud computing, provide promising avenues for handling the vast amounts of sequence data being generated.

History from the 50s to next generation sequencing

In the 1950s, the contemporaneous development of biopolymer sequencing and the digital computer started a digital revolution in the biosciences. Then in the late 1970s, the advent of the personal computer (PC) and Sanger sequencing led to an appreciable amount of sequence data being generated, stored in databases, and conceptualized within a computational framework [1–4]. Communal sequence databases were developed in the 1980s [5, 6], but most investigators worked with data of a scale that allowed transfer to and processing on a local client. In the 1990s, the rise of the Internet facilitated increased data sharing, and analysis techniques began to shift to programs hosted on websites [7]. In the mid-2000s, the most recent big change occurred with the advent of cloud computing and next generation sequencing (NGS), which led to a dramatic increase in the scale of datasets (Fig 1) [4, 8]. This necessitated changes in the storage infrastructure; databases such as the European Nucleotide Archive [9] and the Sequence Read Archive (SRA) [10] were created to store and

Organizing principles for biocomputing history

There are a number of key concepts to keep in mind when considering the coevolution of sequencing and computing. First is the idea that scientific research and computing have progressed through a series of discrete paradigms driven by the technology and conceptual frameworks available at the time, a notion popularized by Jim Gray from Microsoft [12]. Gray organized his views into four paradigms of scientific research. The first two paradigms are empirical observation and attempts to identify general theories. Gray's third paradigm describes the original type of scientific computing, epitomized by large supercomputer-based calculations and modeling, for example, computing a rocket trajectory from a set of equations. This approach tends to favor differential equations and linear-algebraic types of computations.

The fourth paradigm is much more data intensive. Here the "capture, curation, and analysis" of large amounts of information fuels scientific research [12]. Researchers often try to find patterns in "big data" and a premium is placed on resource interoperability and statistical pattern finding. In order to realize fully the potential of this approach to science, significant investment must be made both in the computational infrastructure that supports data processing and sharing and in

* Correspondence: mark@gersteinlab.org

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²Department of Molecular Biophysics and Biochemistry, Yale University, New Haven, CT 06520, USA

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There is always more to the Story..

Muir et al. *Genome Biology* (2016) 17:53
DOI 10.1186/s13059-016-0917-0

Genome Biology

OPINION

Open Access

The real cost of computational generation

Paul Muir^{1,2,3}, Shantao Li⁴, Jing Zhang^{4,5}, George M. W.

Abstract

As the cost of sequencing the amount of sequence data paradigms for data storage increasingly important. These these evolving technologies research moving forward.

History from the 50s to sequencing

In the 1950s, the contemporary polymer sequencing and the digital revolution in the 1970s, the advent of the Sanger sequencing led to a sequence data being generated conceptualized within a communal sequence data 1980s [5, 6], but most in a scale that allowed transfer client. In the 1990s, the increased data sharing, and to shift to programs hosted 2000s, the most recent advent of cloud computing sequencing (NGS), which led the scale of datasets (Fig. changes in the storage infrastructure the European Nucleotide Read Archive (SRA) [10]

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Full list of author information is available at the end of the article

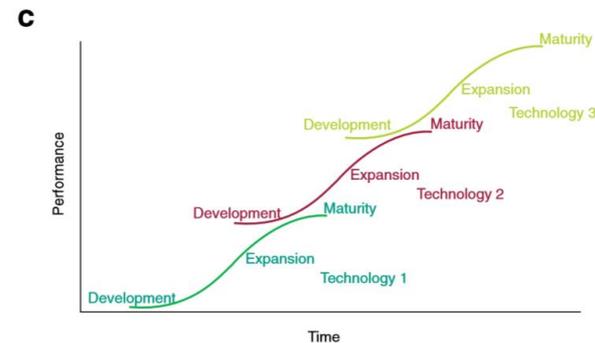
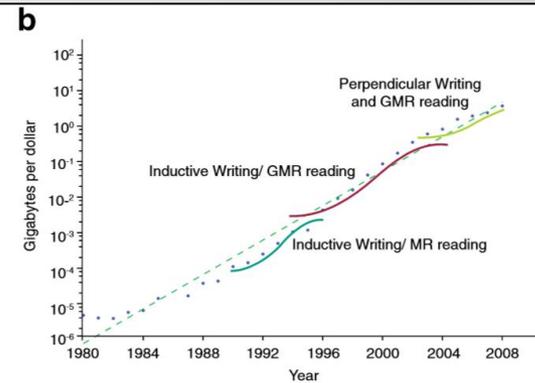
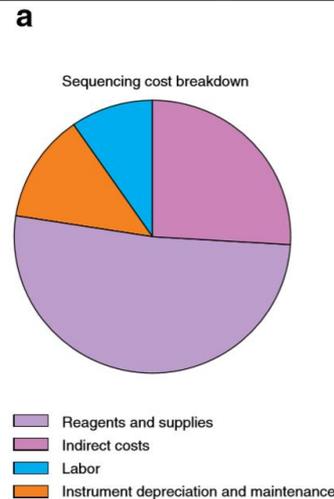
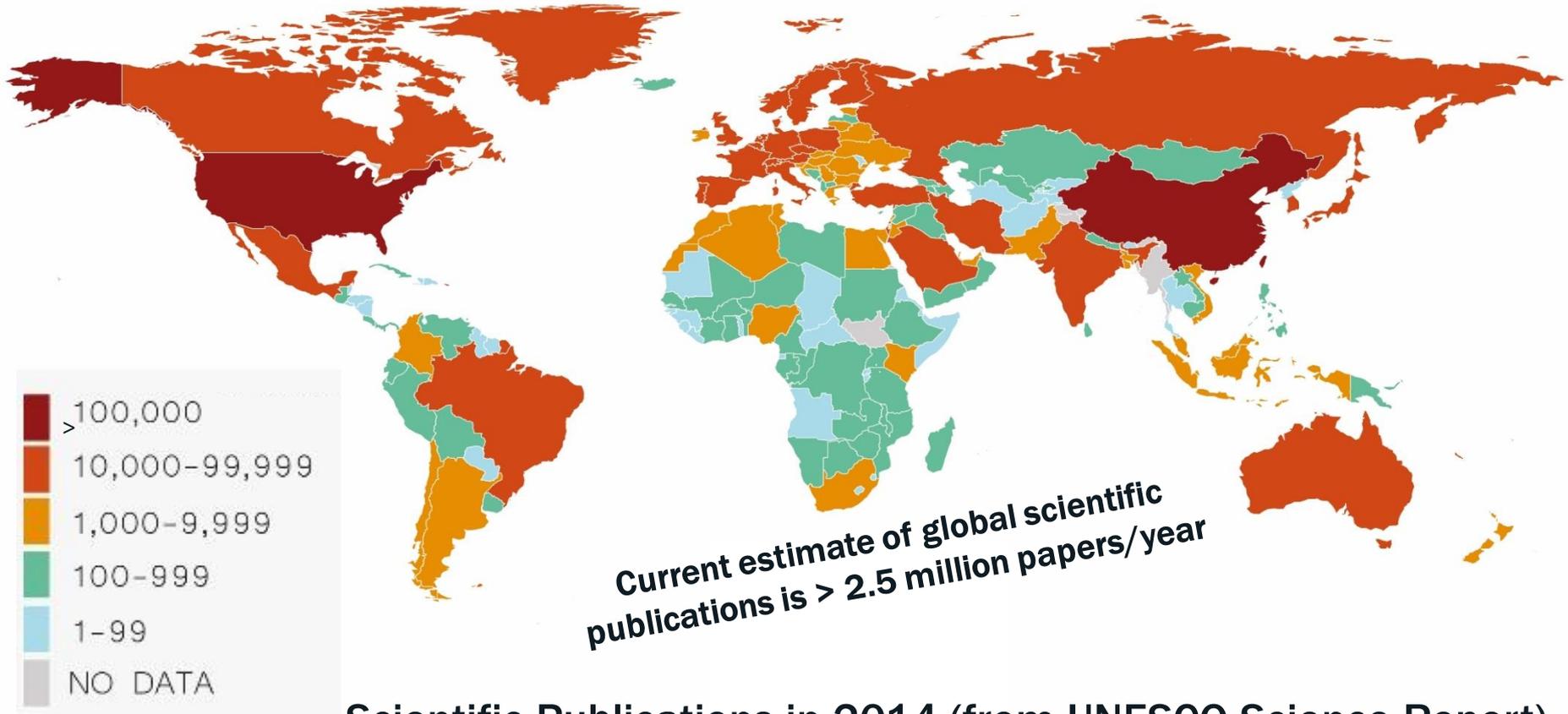


Fig. 2 a The cost breakdown of next generation sequencing projects. The total cost of these projects is split into the cost of labor, reagents and supplies, instrument depreciation and maintenance, and indirect fees. **b** The exponential increase in the number of gigabytes per dollar in hard drive storage technology is due in part to the sequential introduction and improvement of three technologies. Data were obtained from <http://www.mkomo.com/cost-per-gigabyte>. **c** Exponential scaling in technological cost improvement is often the superposition of multiple S-curve trajectories of individual technologies. At the beginning of a technology's life cycle, development costs keep cost reductions low. As the technology matures improvements in production are able to drive down per unit costs and establish an exponential regime. Eventually, the technology reaches maturity where technological limits are encountered and the cost improvements again slow down. GMR reading, Giant Magnetoresistive reading; MR reading, Magnetoresistive reading

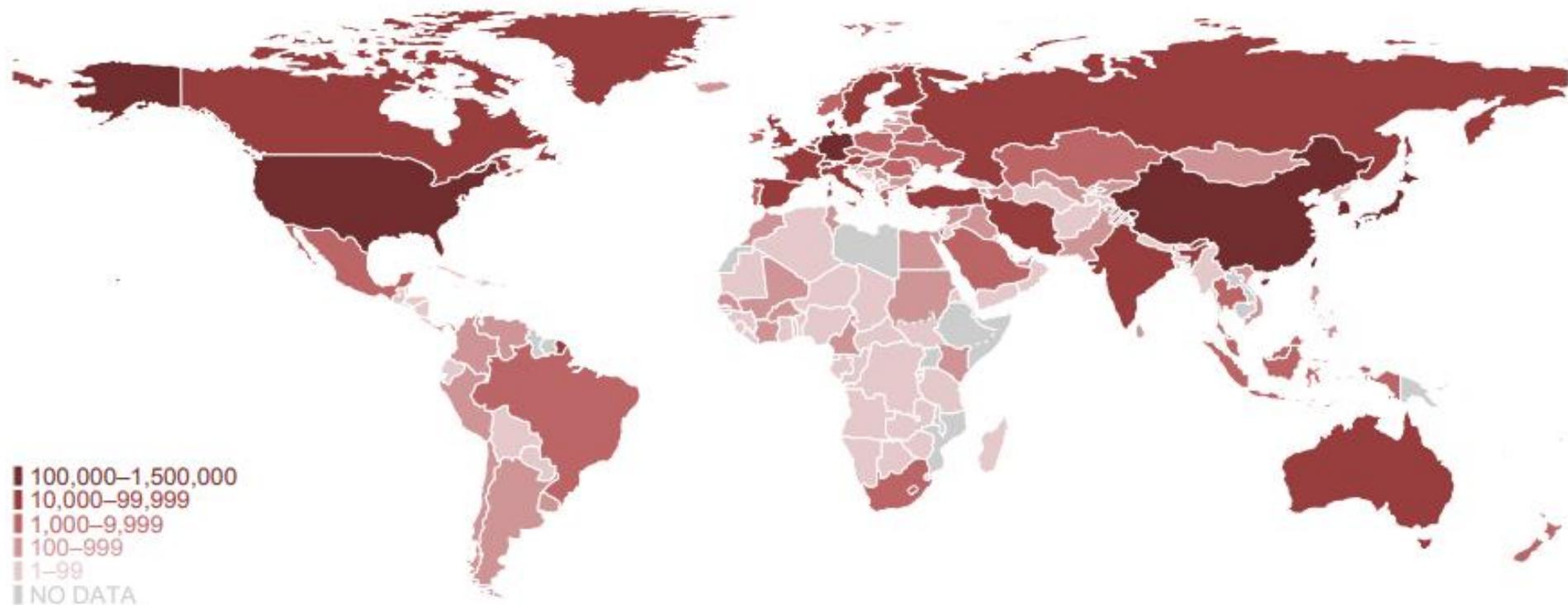
Where are the Rapid Advances in Science Happening?



Scientific Publications in 2014 (from UNESCO Science Report)

Where are the Rapid Advances in Science Happening?

Patent Application by origin 2017



https://www.wipo.int/edocs/pubdocs/en/wipo_pub_941_2018.pdf

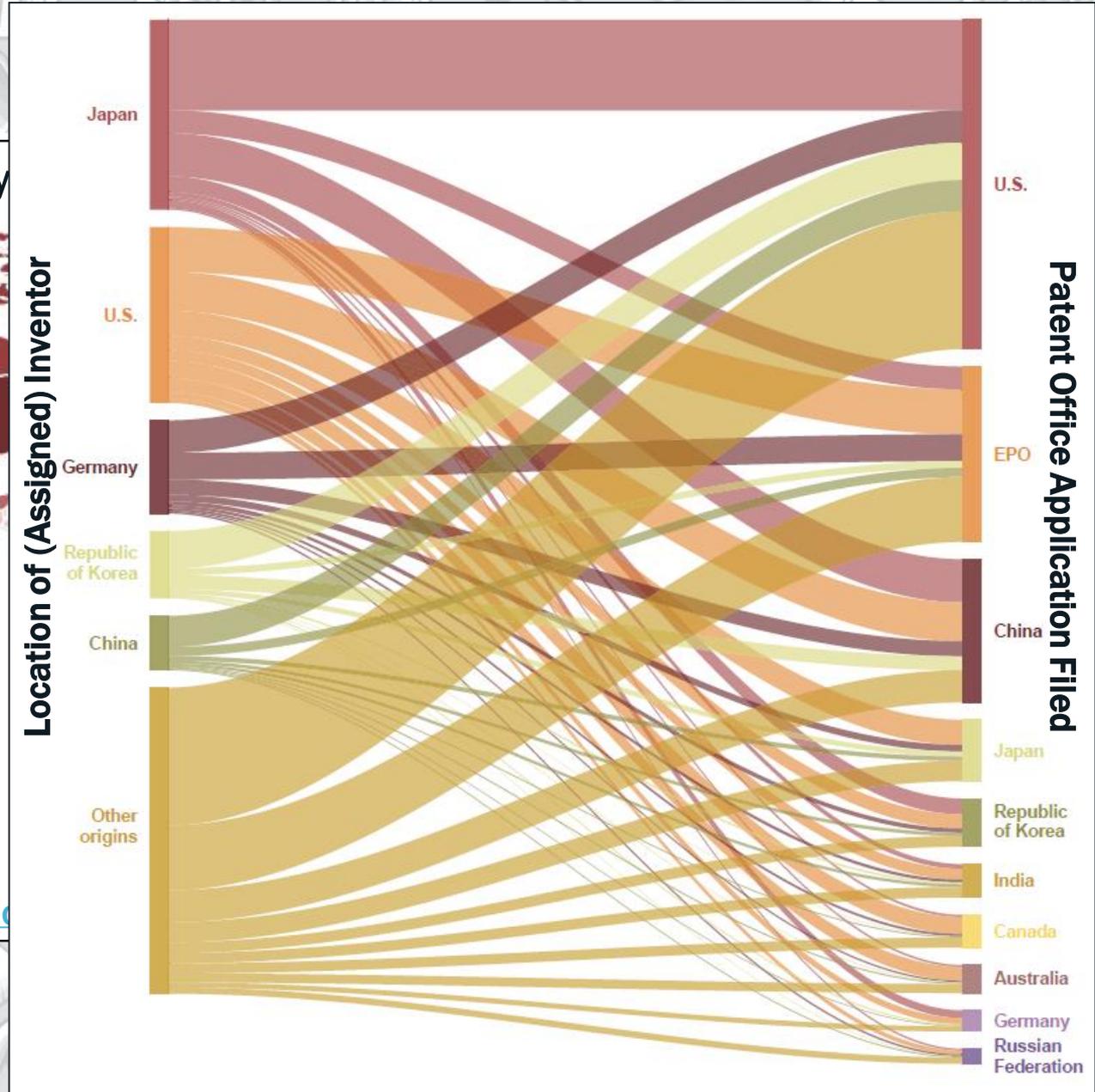
Current estimate of global patent applications is > 3 million/year

Where are the Rapid Advances in Science Happening?

Patent Application by



<https://www.wipo.int/edoc>



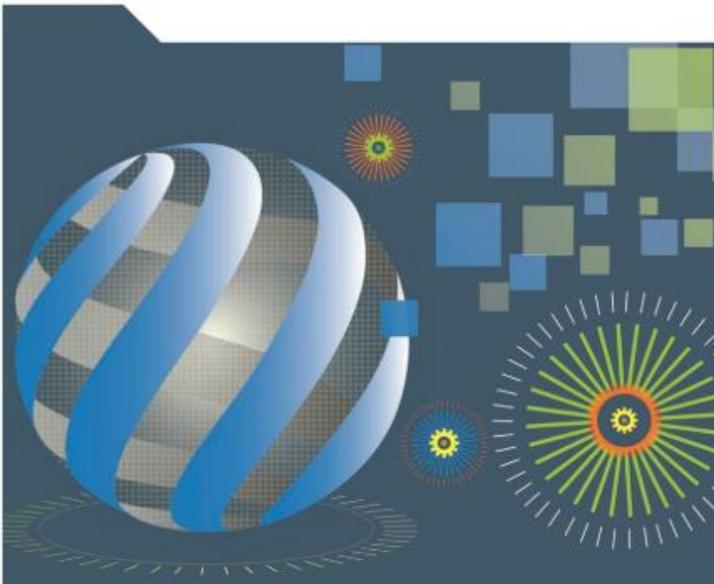
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Where are the Biggest Advances in Science Happening?



OECD Science, Technology and Innovation Outlook 2018

ADAPTING TO TECHNOLOGICAL AND SOCIETAL DISRUPTION



Regulated markets and sectors – commonly operating beyond the borders of the traditional non-proliferation communities



Continuation of driving forces reported in 2016 by OECD

Patent

100,000
10,000
1,000
100-
1-99
NO D

<https://www.wipo.int/edoc>

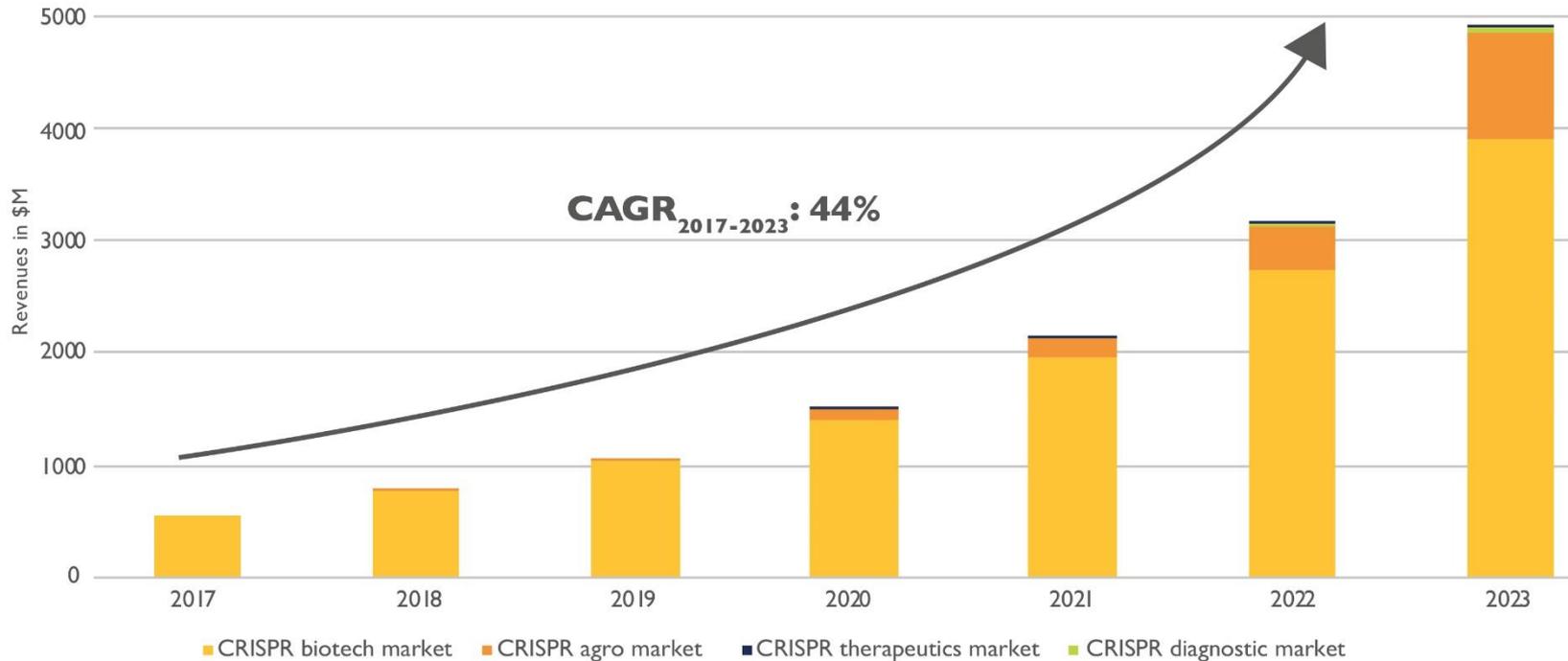
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Commercial/Private Sector Driving Forces are Significant



CRISPR technology: global market forecasts from 2017 to 2023

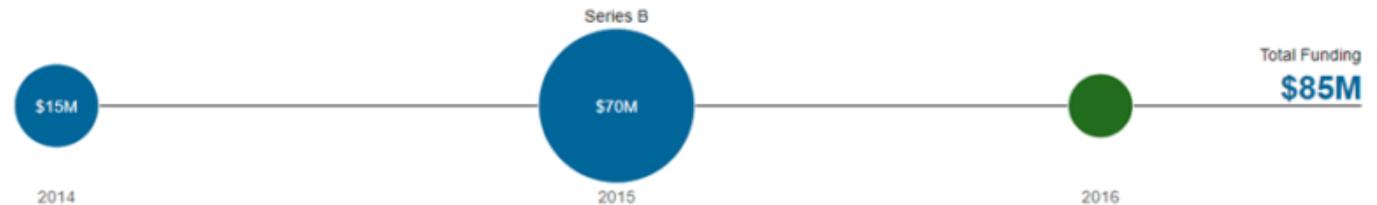
(Source: CRISPR Technology & Market Overview: from Lab to Industry 2018 report, Yole Développement, October 2018)



Commercial/Private Sector Driving Forces are Significant



Top 3 of the most well-funded CRISPR companies



■ CRISPR biotech market
 ■ CRISPR agro market
 ■ CRISPR therapeutics market
 ■ CRISPR diagnostic market

(CAGR = compound annual growth rate)

Commercial/Private Sector Driving Forces are Significant



Top 3 of the most well-funded CRISPR companies



2013



2015

Market capacity
29 November 2019
\$1.5 Billion

Total Funding
\$163M

2016



2014



2015



Market capacity
29 November 2019
\$3.76 Billion

Total Funding
\$162M

2016



2014

Series B



2015

Market capacity
29 November 2019
\$0.83 Billion

Total Funding
\$85M

2016

■ CRISPR biotech market ■ CRISPR agro market ■ CRISPR therapeutics market ■ CRISPR diagnostic market

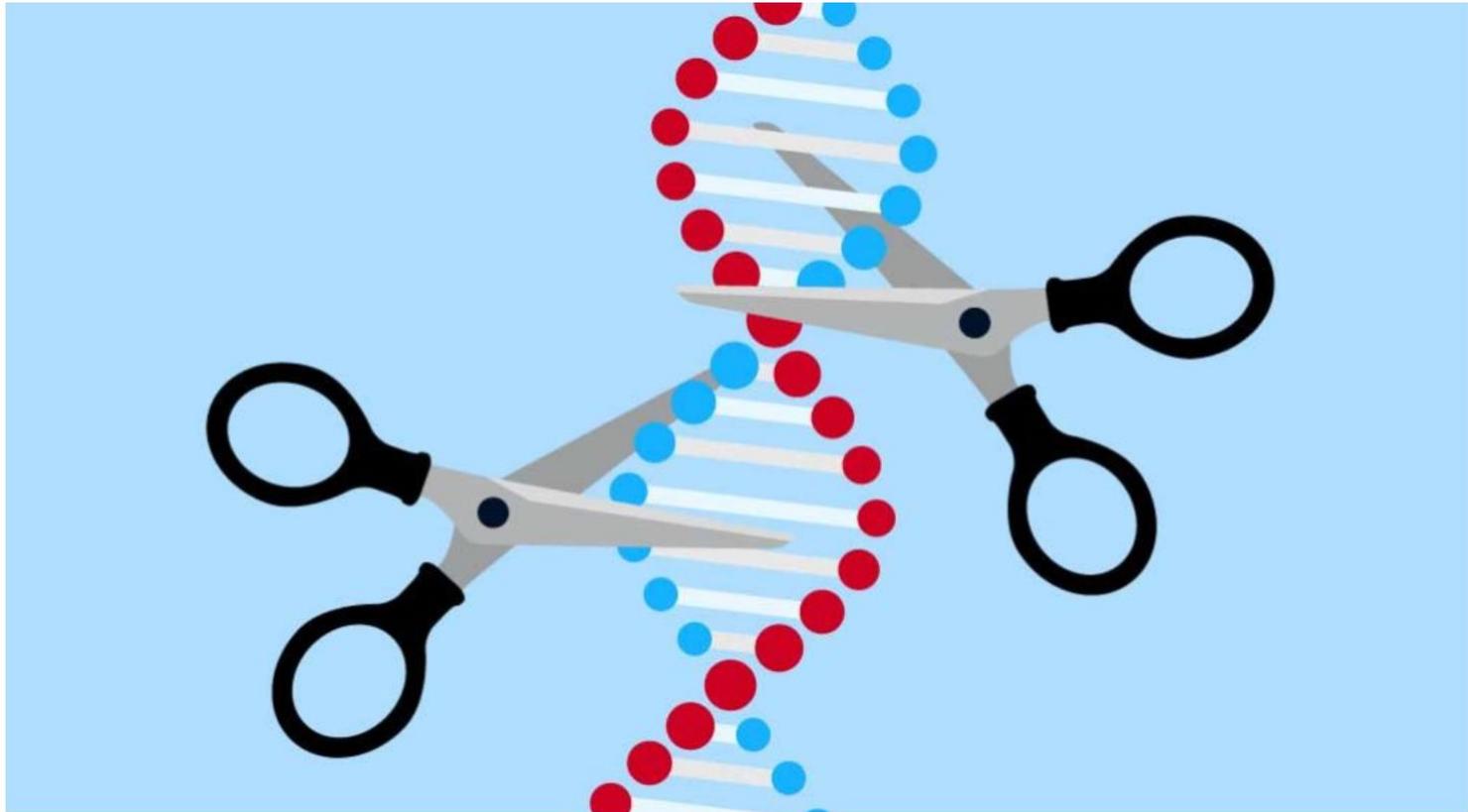
Commercial/Private Sector Driving Forces are Significant

NEWS LIFE

ScienceNews
INDEPENDENT JOURNALISM SINCE 1921

CRISPR enters its first human clinical trials

The gene editor targets cancer, blood disorders and blindness



CUTTING ROOM Scientists will soon wield the molecular scissors CRISPR/Cas9 in the human body. Some people with a form of inherited blindness will have the gene editor injected into their eyes, where researchers hope it will snip out a mutation. Two other trials are CRISPR editing cells outside of the body to treat cancer or blood disorders.

TRAFFIC_ANALYZER/GETTY IMAGES PLUS

Funding
\$3M

Funding
\$62M

Funding
\$35M

(CAGR = compound annual growth rate)

Commercial/Private Sector Driving Forces are Significant

NEWS LIFE

ScienceNews
INDEPENDENT JOURNALISM SINCE 1921

CRISPR enters its first human clinical trials

The gene editor targets cancer, blood disorders and blindness

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Photographer: Dhiraj Singh/Bloomberg

Technology

Crispr's Next Frontier Is In-Human Treatment, Co-Inventor Says

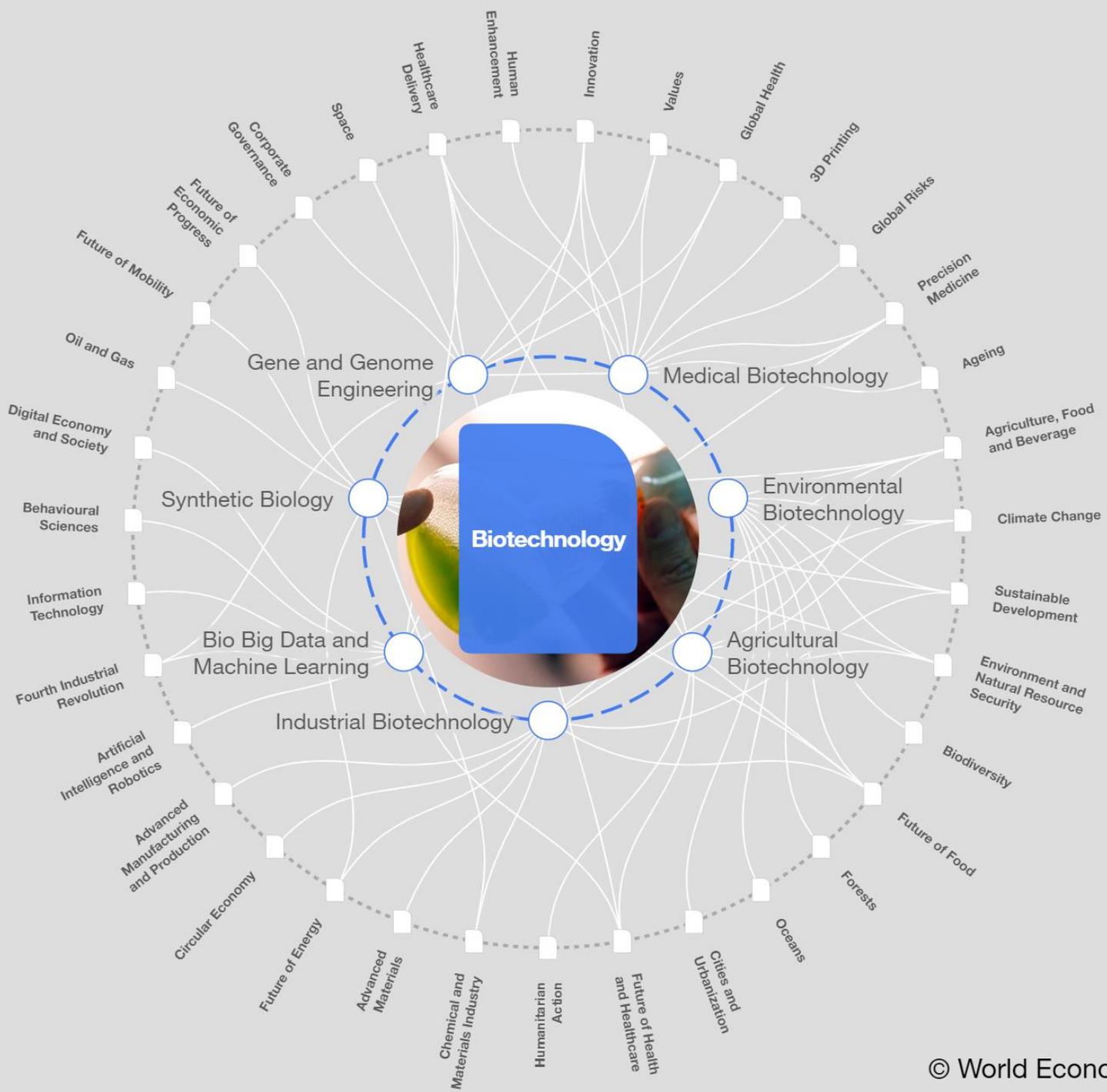
By [Tatiana Darie](#)

October 19, 2019, 4:00 AM PDT

CUTTING ROOM Scientists will soon wield the molecular scissors CRISPR/Cas9 in the human body. Some people with a form of inherited blindness will have the gene editor injected into their eyes, where researchers hope it will snip out a mutation. Two other trials are CRISPR editing cells outside of the body to treat cancer or blood disorders.

TRAFFIC_ANALYZER/GETTY IMAGES PLUS

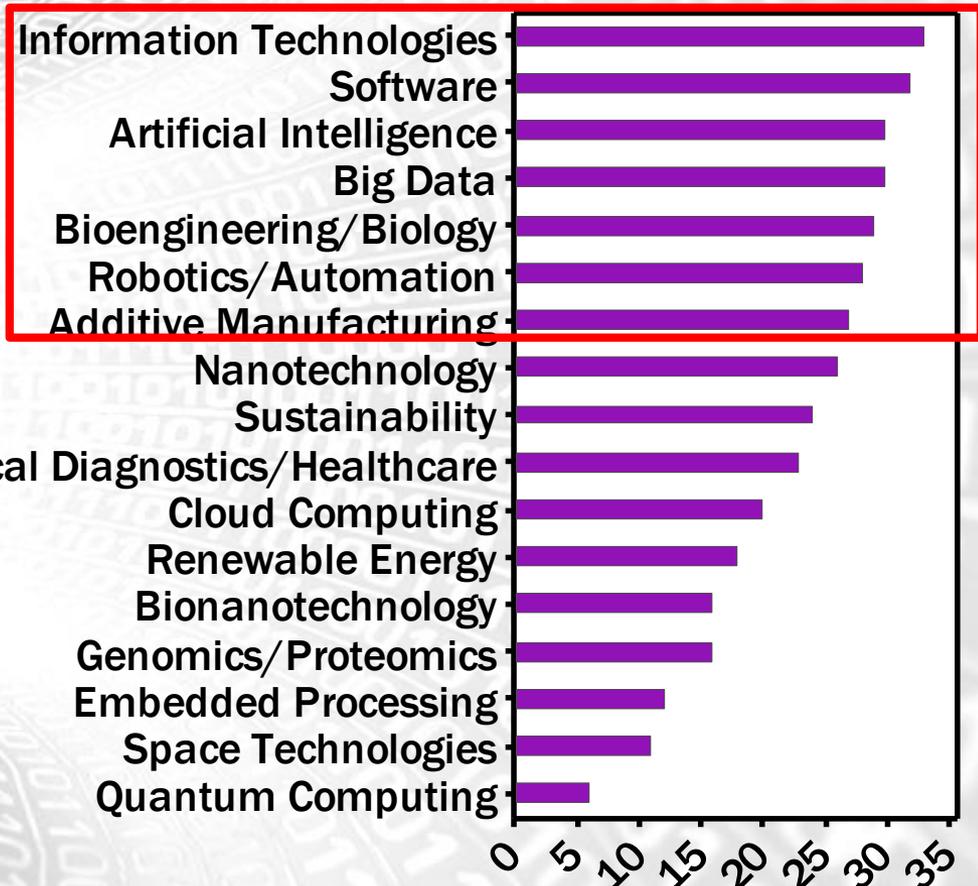
(CAGR = compound annual growth rate)



Technological Change is More Than (Bio)Chemistry

Most important technologies by 2022

Emerging Technologies?

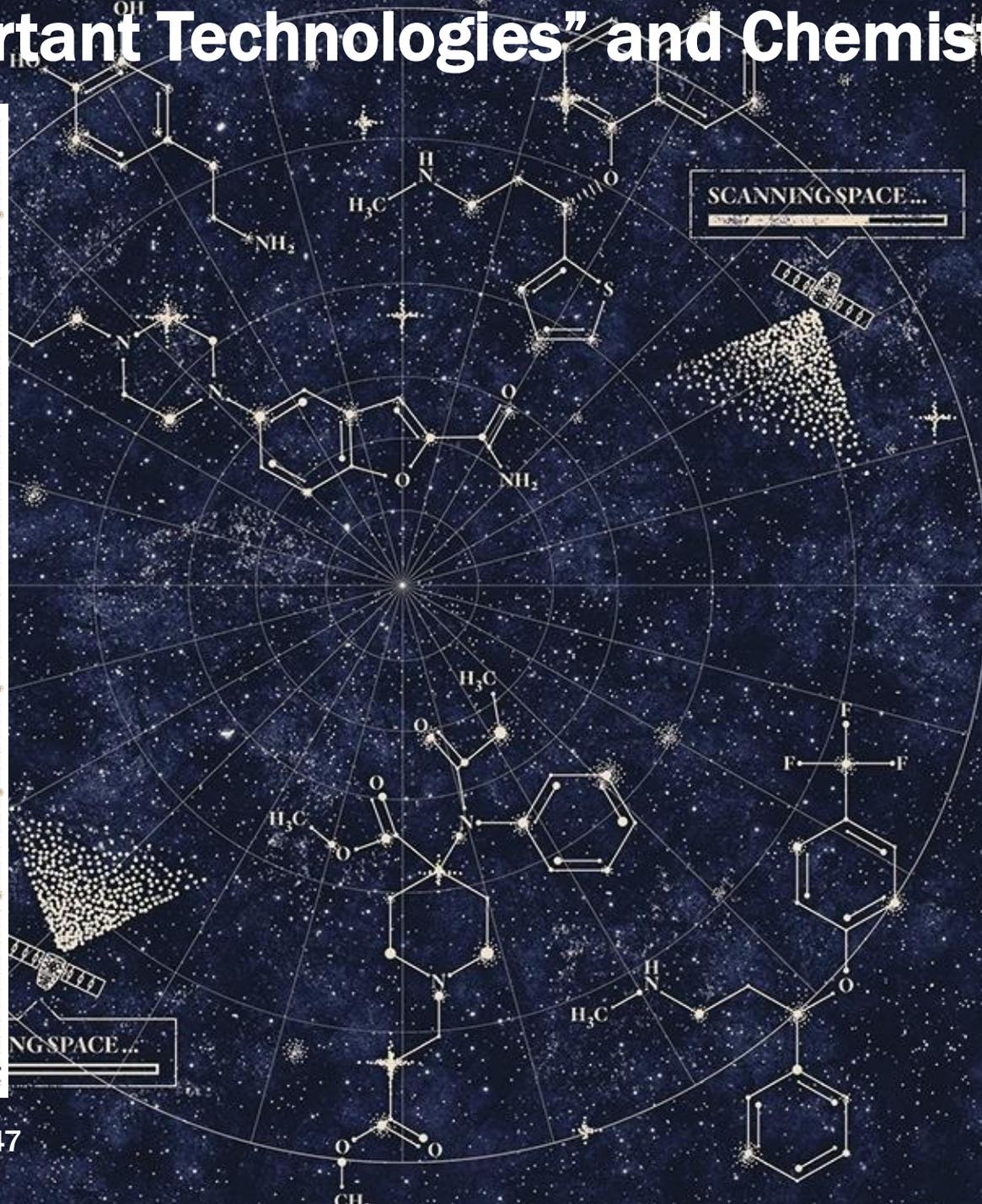
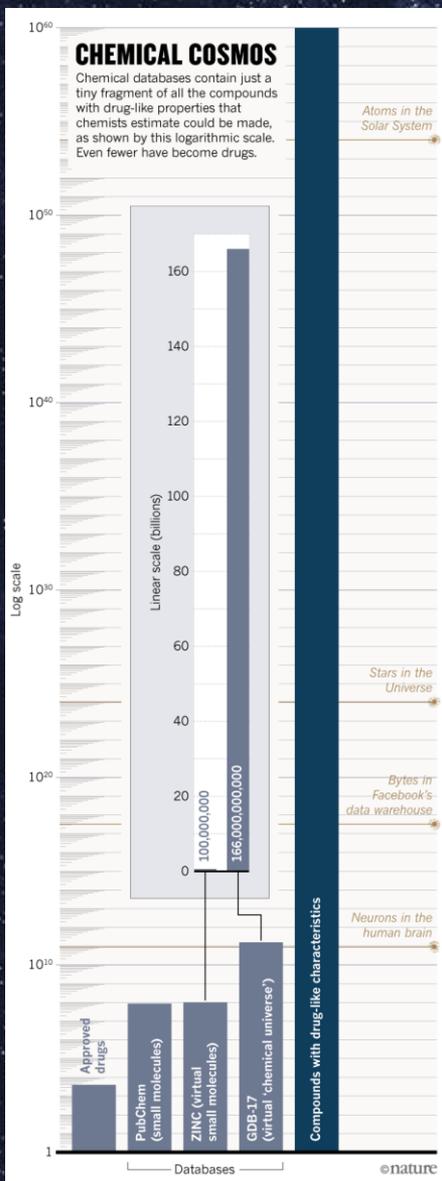


OPCW

These are technologies NOT applications!



“Important Technologies” and Chemistry



“Important Technologies” and Chemistry

Perspective | Published: 15 January 2019

How to explore chemical space using algorithms and automation

Piotr S. Gromski, Alon B. Henson, Jarostaw M. Granda & Leroy Cronin

Nature Reviews Chemistry 3, 119–128 (2019) | Download Citation

Abstract

Although extending the reactivity of a given class of molecules is relatively straightforward, the discovery of genuinely new reactivity and the molecules that result is a wholly more challenging problem. If new reactions can be considered unpredictable using current chemical knowledge, then we suggest that they are not merely new but also novel. Such a classification, however, requires an expert judge to have access to all current chemical knowledge or risks a lack of information being interpreted as unpredictability. Here, we describe how searching chemical space using automation and algorithms improves the probability of discovery. The former enables routine chemical tasks to be performed more quickly and consistently, while the latter uses algorithms to facilitate the searching of chemical knowledge databases. Experimental systems can also be developed to discover novel molecules, reactions and mechanisms by augmenting the intuition of the human expert. In order to find new chemical laws, we must seek to question current assumptions and biases. Accomplishing that involves using two areas of algorithmic approaches: algorithms to perform searches, and more general machine learning and statistical modelling algorithms to predict the chemistry under investigation. We propose that such a chemical intelligence approach is already being used and that, in the not-too-distant future, the automated chemical reactor systems controlled by these algorithms and monitored by a sensor array will be capable of navigating and searching chemical space more quickly, efficiently and, importantly, without bias. This approach promises to yield not only new molecules but also unpredictable and thus novel reactivity.

PERSPECTIVES

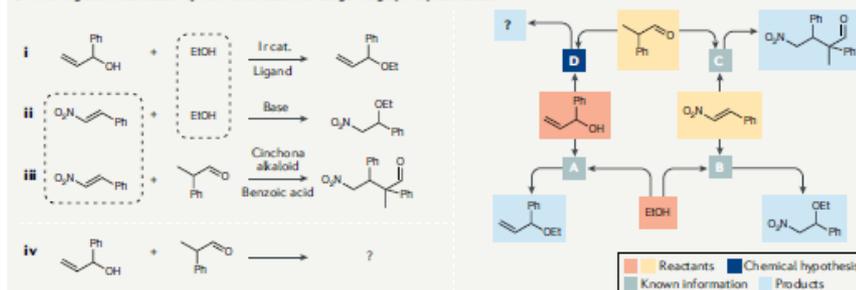
A new approach to materials design for organic light-emitting diodes was demonstrated by Aspuru-Guzik and co-workers using high-throughput virtual screening. By combining theoretical computations, cheminformatics with machine learning and organic

synthesis, it was possible to successfully narrow down the space of 1.6 million possible molecules to thousands of promising novel organic light-emitting diode molecules and then to successfully synthesize new organic light-emitting diodes²⁸.

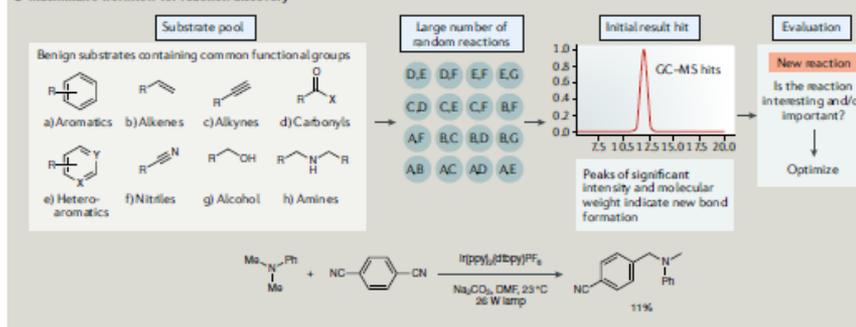
Searching chemical space

Chemical space can be searched for specific molecules or specific goals such as optimized yield or a biological function. This search can be performed through two different avenues: theoretical and experimental. Theoretical searches are an important use

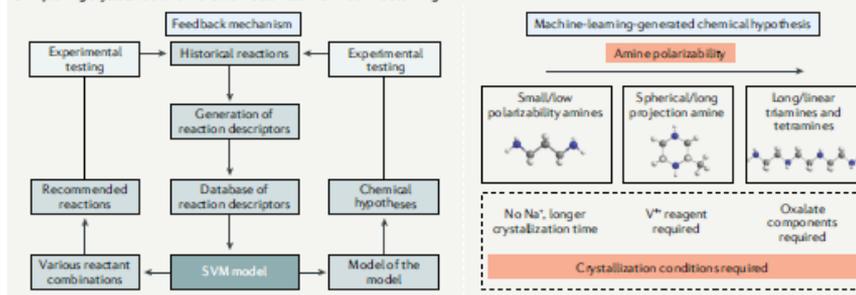
a Inferring chemical reactivity from chemical knowledge via graph representation



b Macmillan's workflow for reaction discovery



c Exploring crystallization of vanadium selenites with machine learning



"Important Technologies" and Chemistry

Perspective | Published: 15 January 2019

How to explore chemical space using algorithms and automation

Piotr S. Gromski, Alon B. Henson, Jaroslaw M. Gra...

Nature Reviews Chemistry 3, 119–128 (2019) | Do...

Abstract

Although extending the reactivity of molecules is relatively straightforward, the discovery of new molecules that result is a whole new world. Reactions can be considered unpredictable, and new knowledge, then we suggest that theoretical approaches are novel. Such a classification, however, is not always being interpreted as unpredictable. The search for new chemical space using automation is a high probability of discovery. The form of the search can be performed more quickly and cost-effectively using algorithms to facilitate the search. Experimental systems can also be designed to generate new molecules, reactions and mechanisms. In order to find new reactions, question current assumptions and explore new areas of algorithmic approaches, and more general machine learning algorithms to predict the chemistry of a reaction that such a chemical intelligence can provide. That, in the not-too-distant future, these systems controlled by these algorithms will be capable of navigating through a vast array of chemical space quickly, efficiently and, importantly, with the promise to yield not only new molecules but also unpredictable and thus novel reactivity.

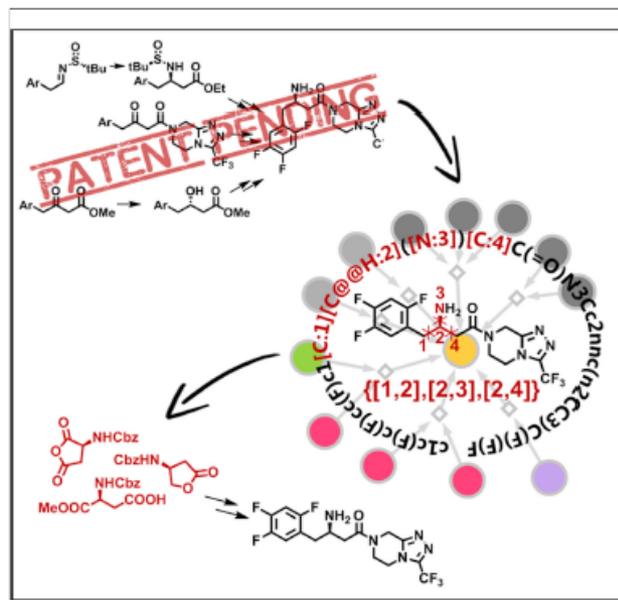
PERSPECTIVES

Chem

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Article

Navigating around Patented Routes by Preserving Specific Motifs along Computer-Planned Retrosynthetic Pathways



Chem 5, 2019, 1–14

DOI: 10.1016/j.chempr.2018.12.004

Karol Molga, Piotr Dittwald,
Bartosz A. Grzybowski

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HIGHLIGHTS

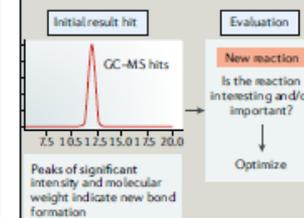
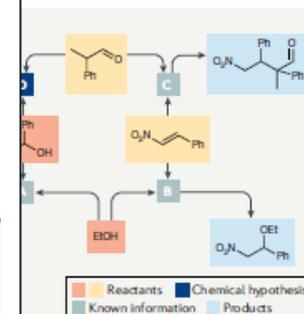
Computer autonomously designs syntheses avoiding desired key disconnections

By doing so, it navigates around patent-protected syntheses of blockbuster drugs

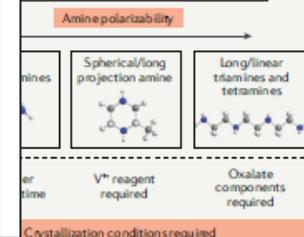
The algorithm can be useful to both identify and prevent such patent "bypasses"

Searching chemical space

Chemical space can be searched for specific molecules or specific goals such as optimized yield or a biological function. This search can be performed through two different avenues: theoretical and experimental. Theoretical searches are an important use



Machine-learning-generated chemical hypothesis



"Important Technologies" and Chemistry

Perspective | Published: 15 January 2019

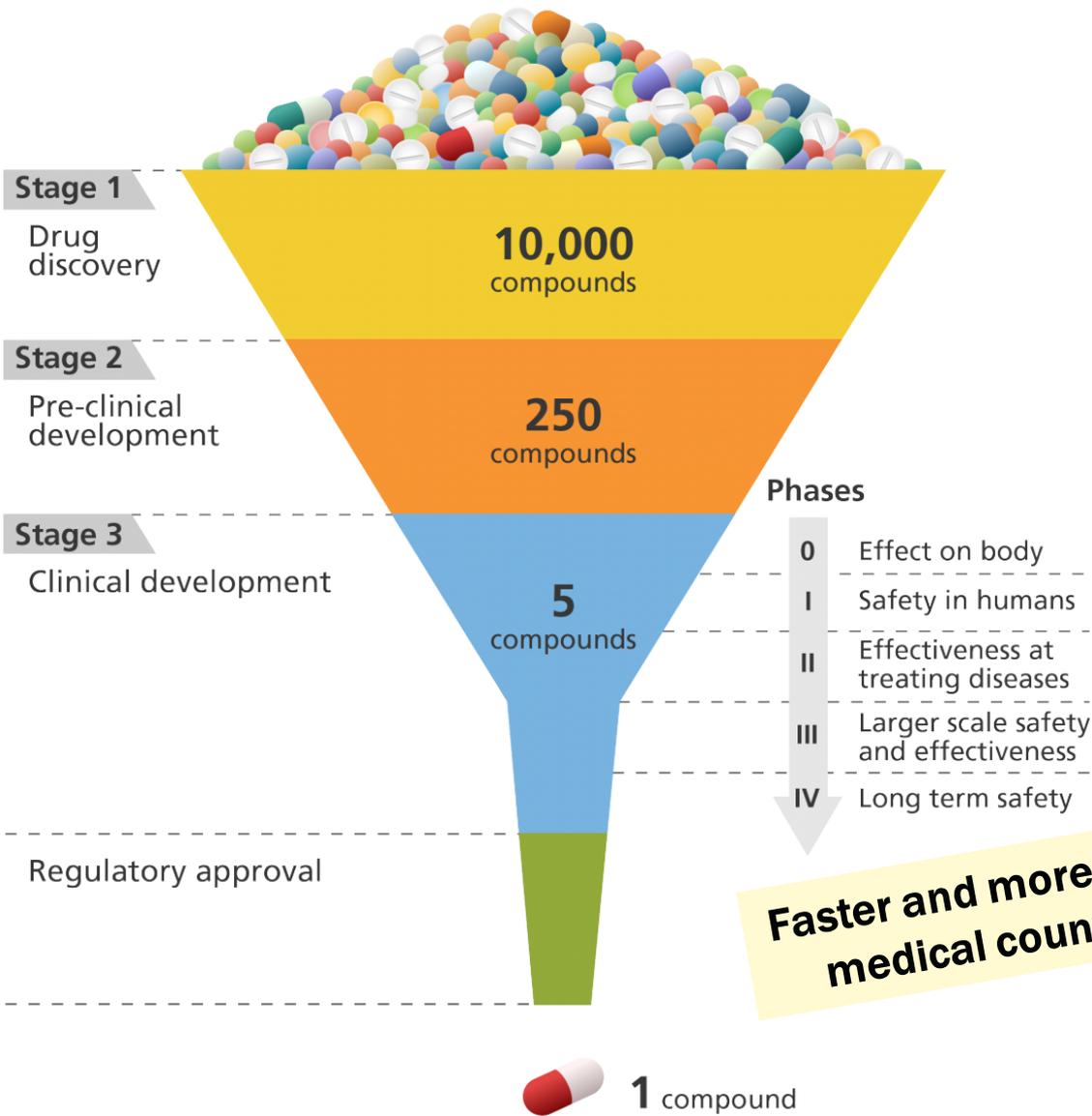
How to algorithm

Piotr S. Gromski,

Nature Reviews C

Abstract

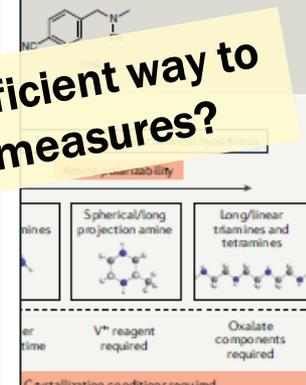
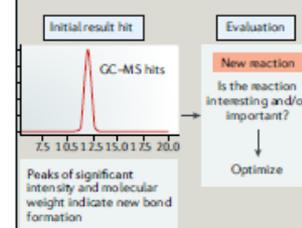
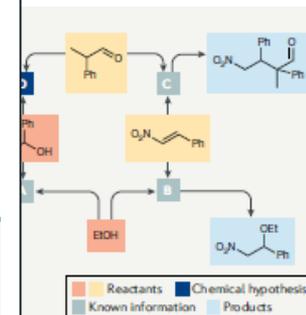
Although relatively the molec reactions knowledg novel. Suc access to being inte chemical probabilit be perform algorithm Experime molecules the huma question using two searches, algorithm that such that, in th systems c array will quickly, e promises to yield not only new molecules but also unpredictable and thus novel reactivity.



Faster and more efficient way to medical countermeasures?

Searching chemical space

Chemical space can be searched for specific molecules or specific goals such as optimized yield or a biological function. This search can be performed through two different avenues: theoretical and experimental. Theoretical searches are an important use



Central Nervous System (CNS)-Acting Chemicals

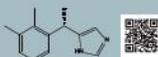


by Sofia Sola Sancho, Maria Hemme and Ayah wafi
Office of the Science Policy Advisor

Toxic chemicals that target the central nervous system (CNS). These chemicals can act as anaesthetics, sedatives, and analgesics. Specific CNS-acting chemicals discussed in the context of the Chemical Weapons Convention have included $\alpha 2$ -adrenergic receptor agonists, inhaled anaesthetics, fentanils and the Schedule 2A.03* chemical BZ.

$\alpha 2$ -adrenergic receptor agonist examples

Dexmedetomidine

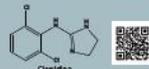


Dexmedetomidine

Mechanism of action:

- Presynaptic activation of the $\alpha 2$ -adrenoceptor, inhibiting norepinephrine release, preventing entry of the neurotransmitter into the synaptic junction (negative feedback).
- Postsynaptic activation of the $\alpha 1$ -adrenoceptor
- Inhibiting sympathetic activity. This results in decreased blood pressure and heart rate.
- Produces analgesic, sedative, and anxiolytic effects.
- Occupational exposure band (OEB 5): control exposure to $< 1 \mu\text{g}/\text{m}^3$.

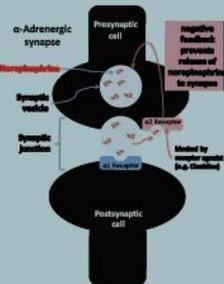
Clonidine



Clonidine

Mechanism of action:

- Reduces release of noradrenaline at both central and peripheral sympathetic nerve terminals
- Produces dose-related sedation, analgesia and anxiolysis.
- A reduction in the effective dose of other anaesthetic agents and opioids is also observed.
- LC_{50} (rat inh): 19.7 $\text{mg}/\text{m}^3/4$ Hours
- LD_{50} (rat iv): 29 mg/kg



Mechanism of action of Dexmedetomidine and Clonidine.

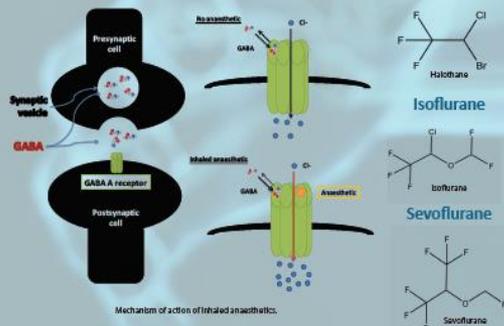
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Inhaled anaesthetic examples

Mechanism of action:

- Enhances γ -aminobutyric acid (GABA) binding to its chloride ion-channel receptor.
- The increase in intra-cellular chloride levels produces an inhibitory effect (anaesthesia).



Mechanism of action of inhaled anaesthetics.

Toxicity Data	Oral LD_{50} (Rat mg/kg)	Oral LD_{50} (Human mg/kg)	Inhalation LC_{50} (Rat ppm)	Oral LD_{50} (Increased SA-ME)	Inhalation LC_{50} (Human ppm)
Halothane	-	8800 mg/kg	29000 (1h)	-	-
Isflurane	1071	4770 $\mu\text{g}/\text{kg}$	18300 (2h)	880	1800
Sevoflurane	-	10800 $\mu\text{g}/\text{kg}$	28000 (2h)	18200	28200

LD_{50} , the lowest dosage of a substance observed to cause a lethality within a specific target population under a specific set of exposure conditions. LC_{50} , the median value of all the observed dosages of a substance resulting in a lethality within a specific target population under a specific set of exposure conditions. LC_{50} , the median value of all the observed concentrations (based on an exposure time of 60 minutes) resulting in a lethality within a specific target population under a specific set of exposure conditions. Labels downward indicate concentration values are derived from specific populations and exposure conditions typically considered animal studies. They may not be representative of all target populations and/or exposure conditions.

Fentanils

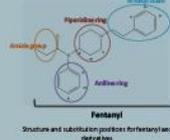
- Fentanils are a highly potent family of opioid narcotic analgesic drugs.
- The family includes fentanyl, a narcotic linked to an increased risk of overdose amongst opioid addicts.
- As of May 2018, there were 20 fentanyl derivatives scheduled under the Single Convention on Narcotic Drugs

Properties

- Fentanyl and its analogues are solids that require aerosolisation for weaponisation purposes.
- Routes of exposure for fentanils include inhalation (aerosolized form), oral exposure or ingestion. Transdermal absorption is possible (for example, the use of transdermal patches), however as the process is slow, such that brief incidental exposures may not cause significant opioid toxicity.



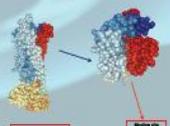
Fentanyl and its analogues have higher potency than morphine and heroin. Poor drug dosage, poly-drug use and addiction are all contributors to the high rates of overdose, respiratory depression.



Structure and substitution positions for fentanyl and derivatives.

Mechanism of action:

- In the CNS, fentanils bind to opioid receptors, specifically μ -receptors. These receptors are found predominantly in the brain and spinal cord
- They act to depress CNS function.
- Bioavailability from inhalation exposure can range from 12-100%.



Crystal structure of the μ -opioid receptor bound to a morphinan antagonist (PDB: 6D06; Data Bank: Structure: 4OJ4)

Effects:

- Loss of pain sensation
- Miosis
- Decreased intestinal peristalsis (constipation)
- Nausea and vomiting
- Dose-dependent respiratory depression (which can lead to death)
- Diminished mental alertness resulting in a feeling of drowsiness, euphoria, sleepiness, and unconsciousness



Antidotes: Naloxone hydrochloride (Narcan) or Naltrexone

- Opioid receptor antagonists.
- Bind to the opioid receptors more strongly than a fentanyl derivative, but do not activate the receptor.
- Quickly reverse signs and symptoms, especially life-threatening respiratory depression.
- Short half-life; symptoms may return in an apparently stabilized patient and antidotes might need to be readministered.
- 0.4 mg is the standard starting dose but for some fentanyl derivatives doses up to 2 mg have been required.



Time Weighted Average - Occupational Exposure Limits (OEL-TWA)	
Alfentanil	1 $\mu\text{g}/\text{m}^3$
Fentanyl	0.1 $\mu\text{g}/\text{m}^3$
Sufentanil	0.022 $\mu\text{g}/\text{m}^3$



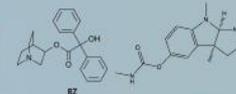
BZ (3-quinuclidinyl benzilate)

BZ is a glycolate anticholinergic compound and is a only "CNS-acting chemical" found in the Annex of Chemicals of the Chemical Weapons Convention (Schedule 2A.03*).



Properties

- Odourless crystalline powder with bitter taste.
- Persistent in soil and water and on most surfaces.
- Half-life in moist air ~ 3-4 weeks.



BZ

Antidote: Physostigmine

- Temporarily raises acetylcholine concentrations by binding reversibly to anticholinesterase.



Safety Ratio of BZ



The large difference between the median lethal concentration (LC_{50}) and the median incapacitating concentration (IC_{50}) allows for the onset of CNS-acting symptoms to appear at a dosage much lower than a lethal dose.



Dose in [$\text{mg}/\text{min}/\text{m}^3$]

Mechanism of action:

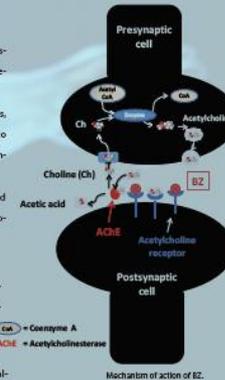
- Acts as a competitive inhibitor of the neurotransmitter acetylcholine (ACh) in postsynaptic ACh receptors.
- As the concentration of BZ at these sites increases, the proportion of receptors available for binding to acetylcholine decreases, resulting in an understimulation of nerve signal transduction.
- When administered by inhalation (in aerosolized form), absorption to the bloodstream is more pronounced than with oral administration.

CNS effects:

- Stupor, ataxia, confusion, and combativeness. Induces concrete and paranoid illusions and hallucinations.

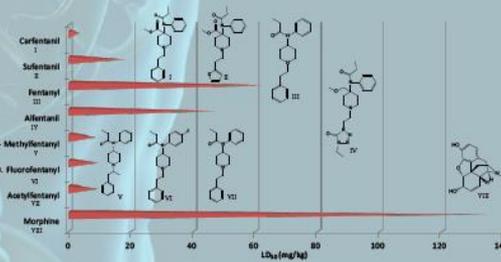
Peripheral effects:

- Mydriasis, blurred vision, dry mouth and skin, initially rapid heart rate; later, normal or slow heart rate.



Mechanism of action of BZ.

Toxicity



Industry 4.0 and the chemicals industry

READY TO BE DEPLOYED NOW



Virtual assistants (natural language based)



Datascience-based maintenance



AI-based pricing engines



Blockchain-based supply chain track & trace



AI-based next best actions in marketing



Virtual assistant-based internal administration



AI-based augmentation of control room operators



Robotic process automation in administration



AI-based experiment prediction & evaluation

...and so much more...

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**New ways to approach problem solving
and change organizational cultures!**



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With a “physical” location and real equipment and people to maintain it!



Does it Look Like a Contract Research Organization?
This is not a new thing! Perhaps the answers to concerns about this are found in existing business models of CRO's?

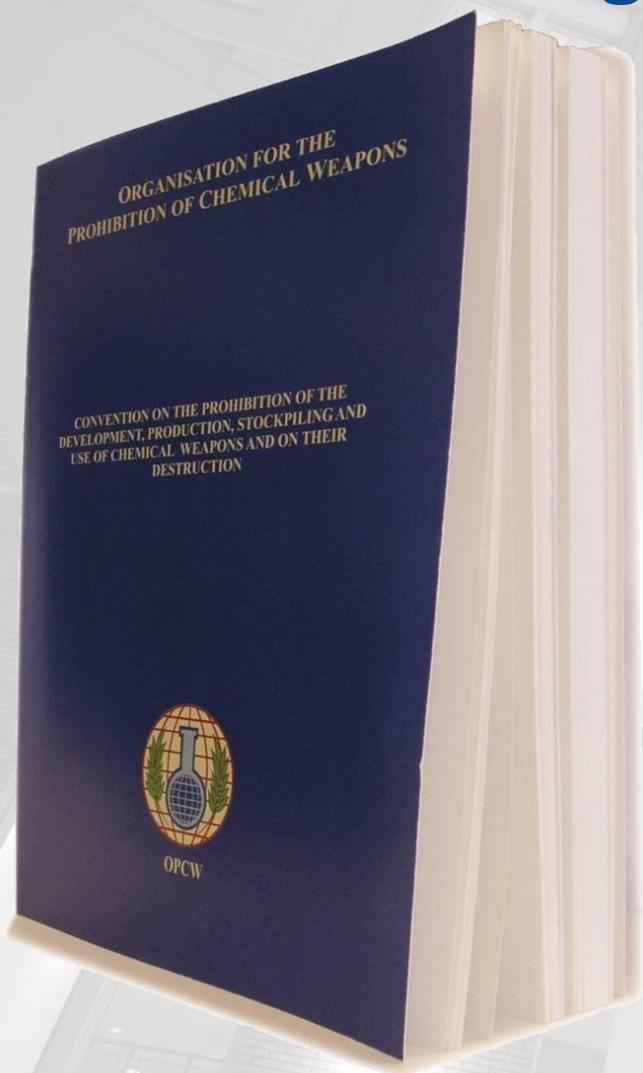
Contract Research Services

Timing Is Everything!

Policy, Regulation and/or Oversight for Science?



International Obligations and Member State Compliance



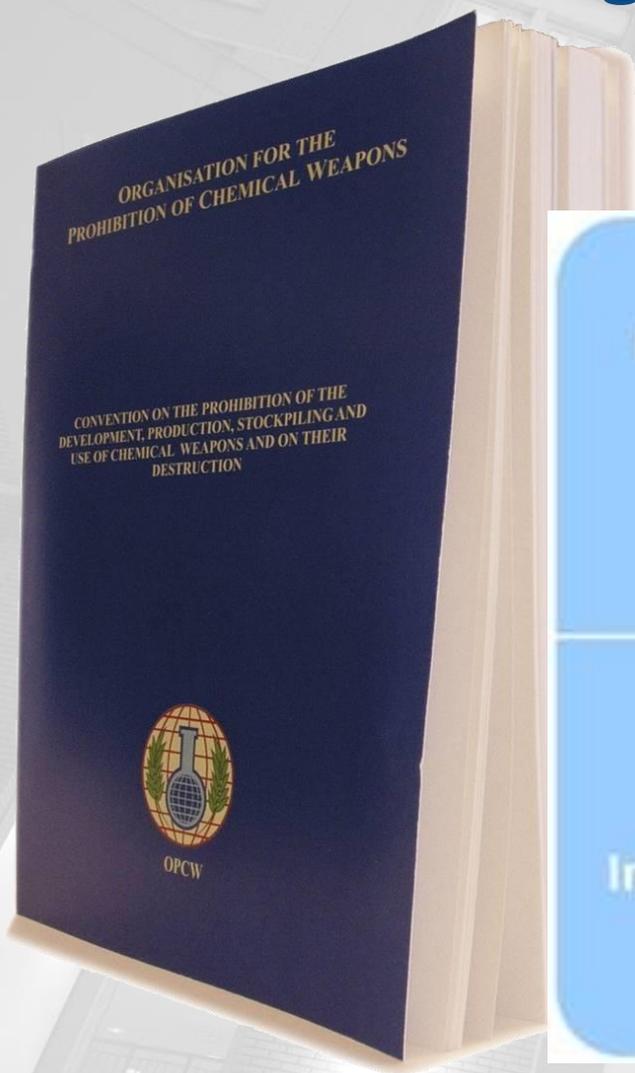
- **Treaty = Agreement between states**
- **National Compliance = laws and regulations**
 - **States Parties must establish a “National Authority”**
 - **National legislation**
 - **Criminal laws, trade monitoring, reporting and enforcement**



OPCW

International Obligations and Member State Compliance

- **Treaty = Agreement between states**



We Cannot Afford to Fear Science!



All of this Advanced Science and...

- Chemical weapons being used



All of this Advanced Science and...

- Chemical weapons being used



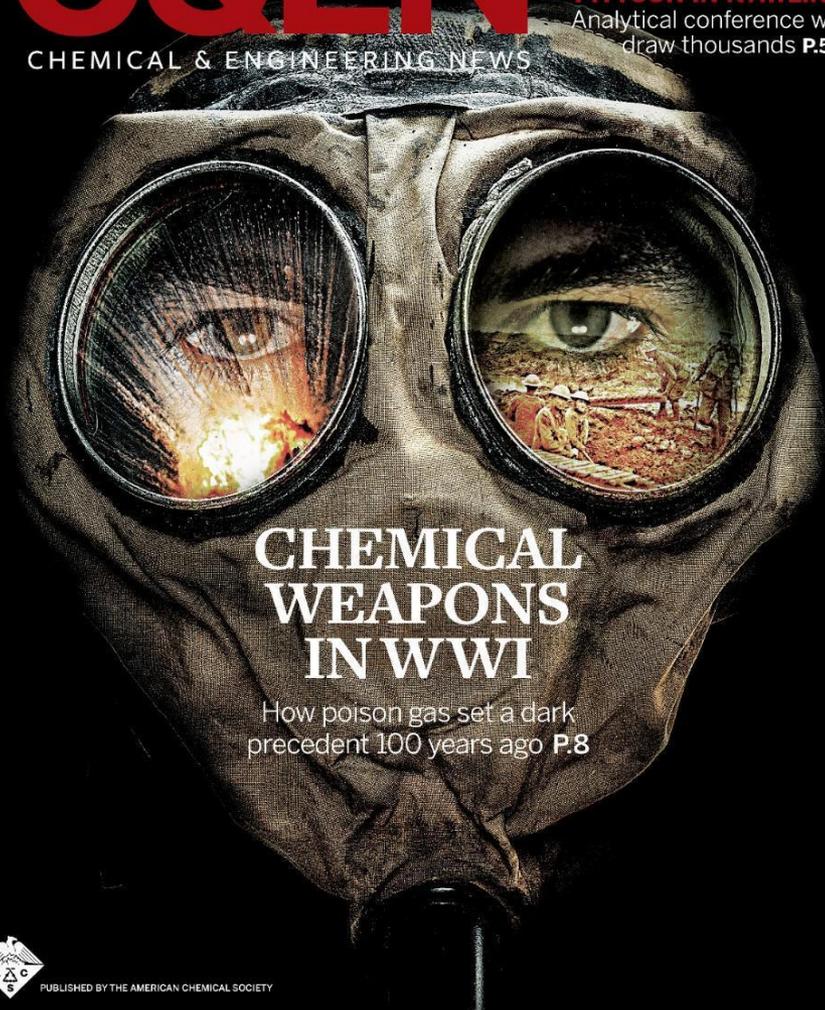
FEBRUARY 23, 2015

C&EN

CHEMICAL & ENGINEERING NEWS

FINE CHEMICALS
Nonpharma business rules
InformEx show **P.24**

PITTCON IN N'AWLINS
Analytical conference will
draw thousands **P.50**



CHEMICAL WEAPONS IN WWI

How poison gas set a dark
precedent 100 years ago **P.8**



PUBLISHED BY THE AMERICAN CHEMICAL SOCIETY



All of this Advanced Science and...

■ Chemical weapons being used

■ Biological weapons being used?



FEBRUARY 23, 2015

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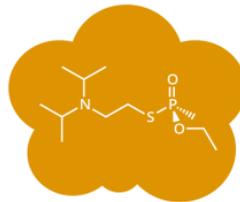
FINE CHEMICALS
Nonpharma business rules
InformEx show **P.24**

PITTCON IN N'AWLINS
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draw thousands **P.50**

CHEMICAL WARFARE NERVE AGENTS

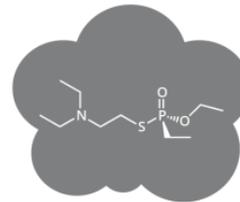
PART TWO: THE V SERIES

THE V SERIES NERVE AGENTS ARE HIGHLY TOXIC CHEMICAL WARFARE AGENTS. THE 'V' STANDS FOR 'VENOMOUS'. THEY WERE DISCOVERED IN THE UK IN THE 1950s, AND LATER VX WAS DEVELOPED FOR MILITARY USE BY THE UNITED STATES, THOUGH IT HAS NEVER BEEN USED IN WARFARE.



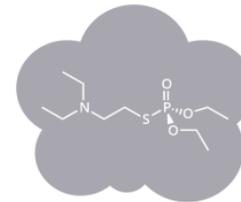
VX

O-Ethyl S-[2-diisopropylaminoethyl] methylphosphonothioate (the compound known as 'Russian VX' is an isomer of this compound)



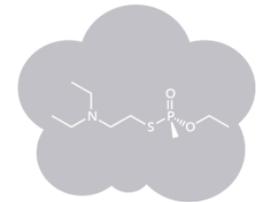
VE

O-Ethyl S-[2-diethylaminoethyl] ethylphosphonothioate



VG

O,O-Diethyl S-[2-diethylaminoethyl] phosphorothioate



VM

O-Ethyl S-[2-diethylaminoethyl] methylphosphonothioate

SMELL & APPEARANCE

VX

Pure VX is a colourless liquid, but more commonly it is an amber-coloured, oily, odourless liquid.

VE

VG

VM

The other V series nerve agents are thought to be odourless, colourless liquids at room temperature (when pure). As they have not been studied in detail outside of military investigations as to their usefulness in warfare, little more is known about them.

Generally, their volatilities are low, though VX is the member of the series with the lowest volatility.

DISCOVERY

**1952-1955
UNITED KINGDOM**

The V series nerve agents were discovered during work to synthesise pesticides and insecticides. VG was originally sold as an insecticide, under the name 'Amiton'. It was marketed from 1954, but later withdrawn after the issues with human toxicity became apparent.

UK research on the compounds stopped in 1956, but was traded with the US in exchange for information on building thermonuclear devices.

USAGE & FATALITIES



As the V series agents exist primarily as low volatility liquids, they are designed for use as area-denial agents.



The only recorded human fatality as a result of VX is in Japan in 1994, when a sect used it to assassinate a former member. It may have also been used in Iraq by Saddam Hussein, though there is no conclusive evidence.



Sheep fared less well: Over 6000 were killed or injured in 1968 after a test in Utah, USA, with leftover VX leaking from a dispenser suggested as the likely accidental cause.

Production of VX was banned in the US in 1969. Its production and stockpiling was outlawed worldwide in 1993.

LETHALITY

FIGURES FOR VX

median lethal concentration

15

milligram-minutes per cubic metre

median lethal dose

10

milligram-minutes per person (skin exposure)

Due to the scarcity of research on the V series nerve agents, data on lethality is only reliably available for VX. The other V series agents are thought to have roughly similar toxicities.

They have low volatilities - VX is around 2000 times less volatile than sarin - so the primary method of exposure is often through skin contact, rather than inhalation.

EFFECTS OF NERVE AGENTS



Inhibit breakdown of acetylcholine



Cause contraction of the pupils



Excessive mucus, tears, saliva & sweat



Nausea, gastrointestinal pain & vomiting



Bronchoconstriction & chest tightness



Spasms, convulsions & loss of bowel control



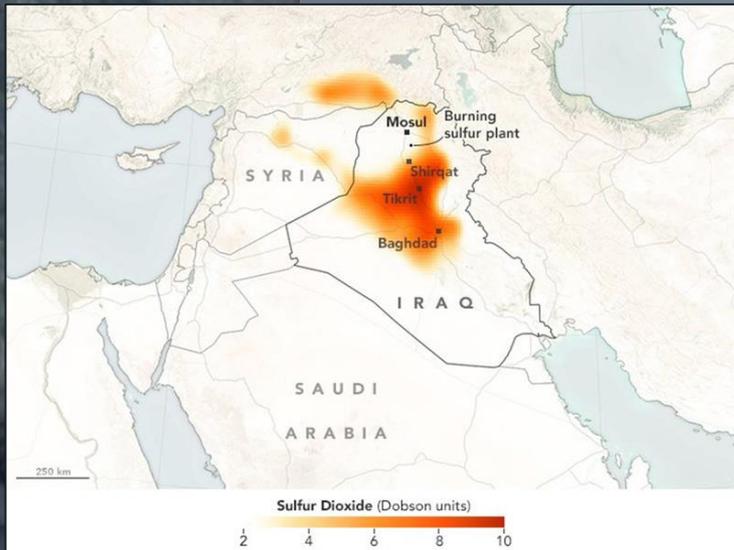
Coma & eventual death



All of this Advanced Science and...

■ Chemical weapons being used

■ Biological weapons being used?



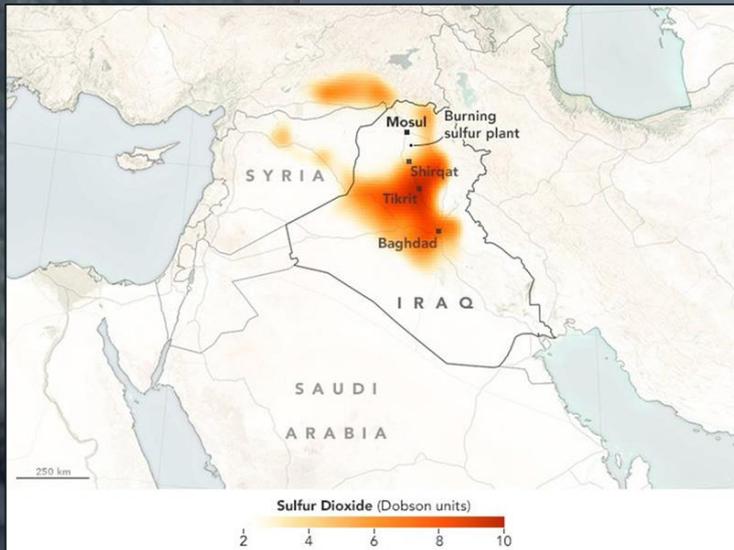
- TS
- Inhibit breakdown of acetylcholine
- Cause contraction of the pupils
- Excessive mucus, tears, saliva & sweat
- Nausea, gastrointestinal pain & vomiting
- Bronchoconstriction & chest tightness
- Spasms, convulsions & loss of bowel control
- Coma & eventual death



All of this Advanced Science and...

- Chemical weapons being used

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All of this Advanced Science and...

- C
- B
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- IS : Inhibit breakdown of acetylcholine
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CONSENSUS STUDY REPORT

Reproducibility and Replicability in Science



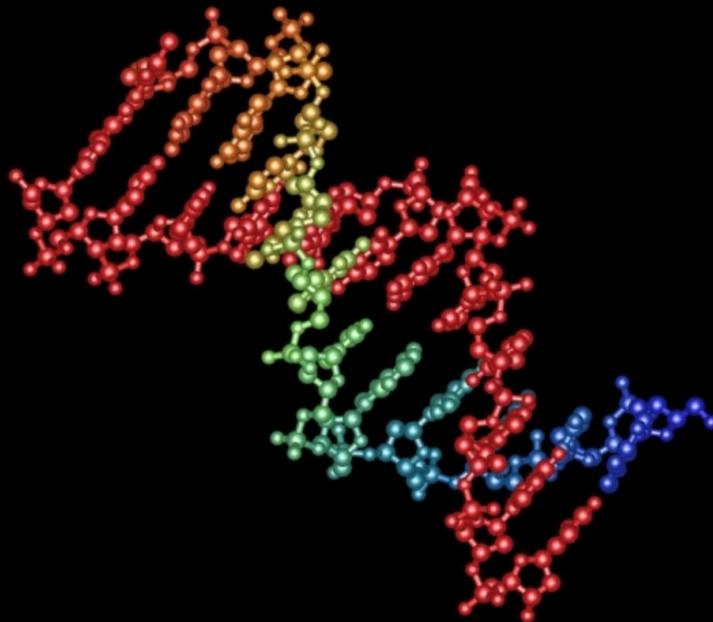
MIT News

ON CAMPUS AND AROUND THE WORLD

Browse

or

Search



A new technique developed at MIT can edit DNA in precise locations.

Graphic: Christine Daniloff/iMol

Editing the genome with high precision

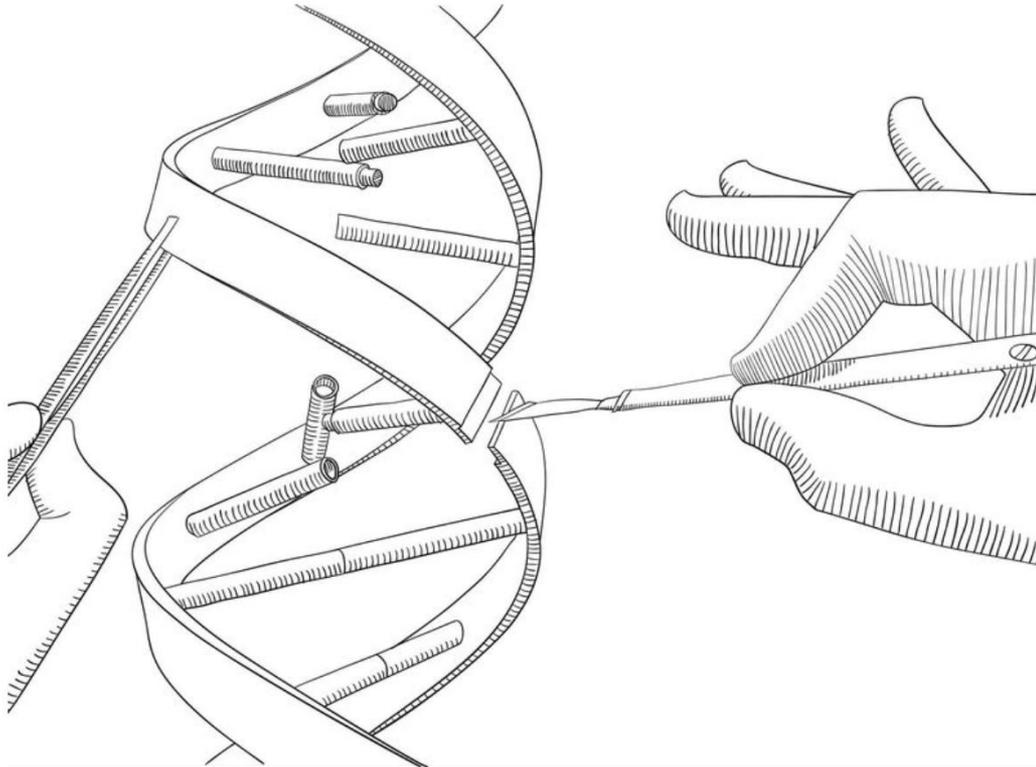
New method allows scientists to insert multiple genes in specific locations, delete defective genes.

Anne Trafton, MIT News Office
January 3, 2013

PRESS MENTIONS

A New Gene Editing Tool Could Make CRISPR More Precise

Prime editing offers a new way to make changes to DNA while avoiding some of the drawbacks and clunkiness of traditional CRISPR



Unlike classic CRISPR-based editing, which fully cleaves DNA in two, prime editing starts with a cut to only one strand of the double helix. (Perception7 / iStock)

By [Lila Thulin](#)
SMITHSONIAN.COM
OCTOBER 21, 2019

January 8, 2018



Browse or Search

A new technique developed at MIT can edit DNA in precise locations.

Graphic: Christine Daniloff/iMol

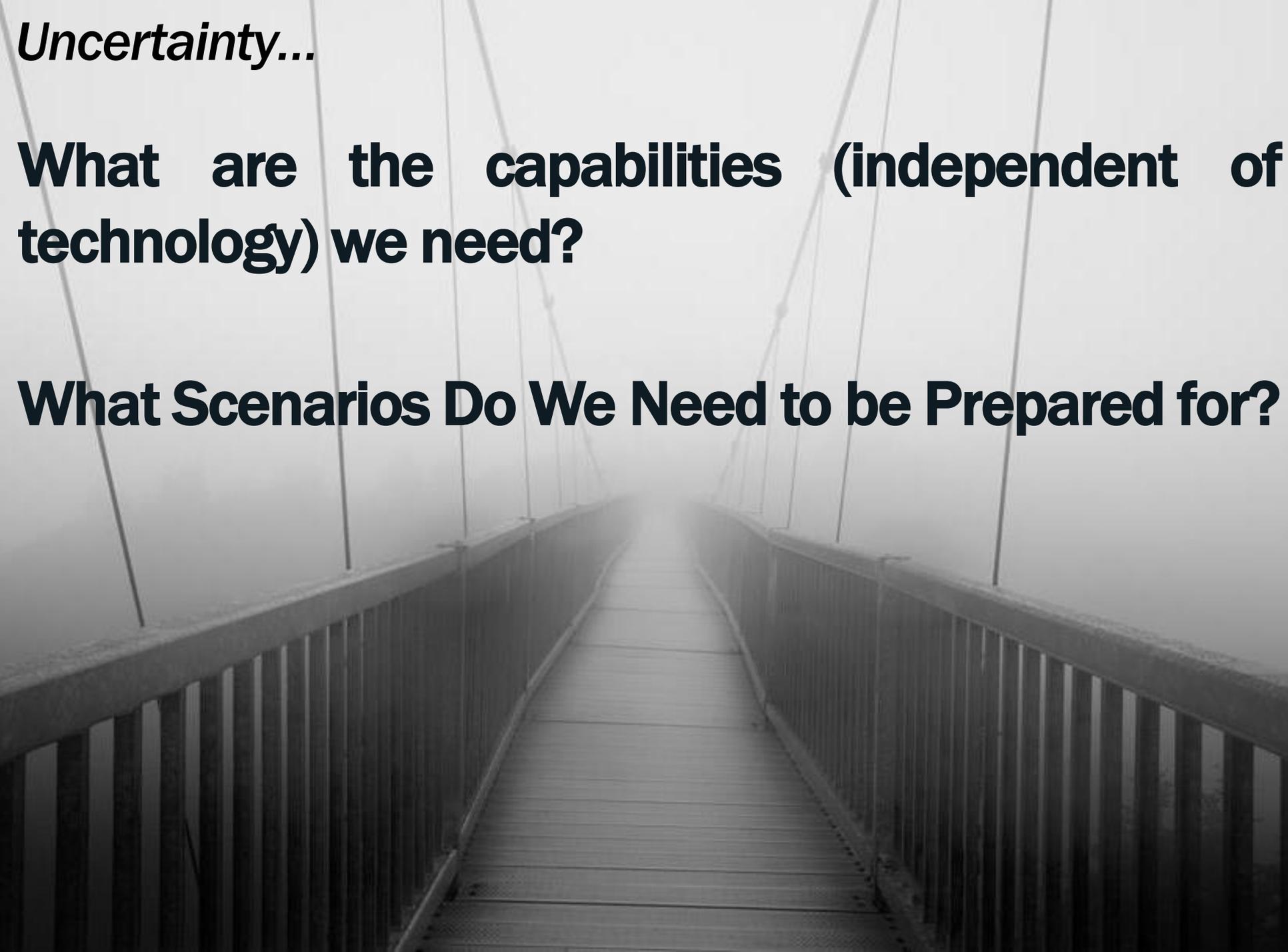
h precision
ple genes in specific locations, delete

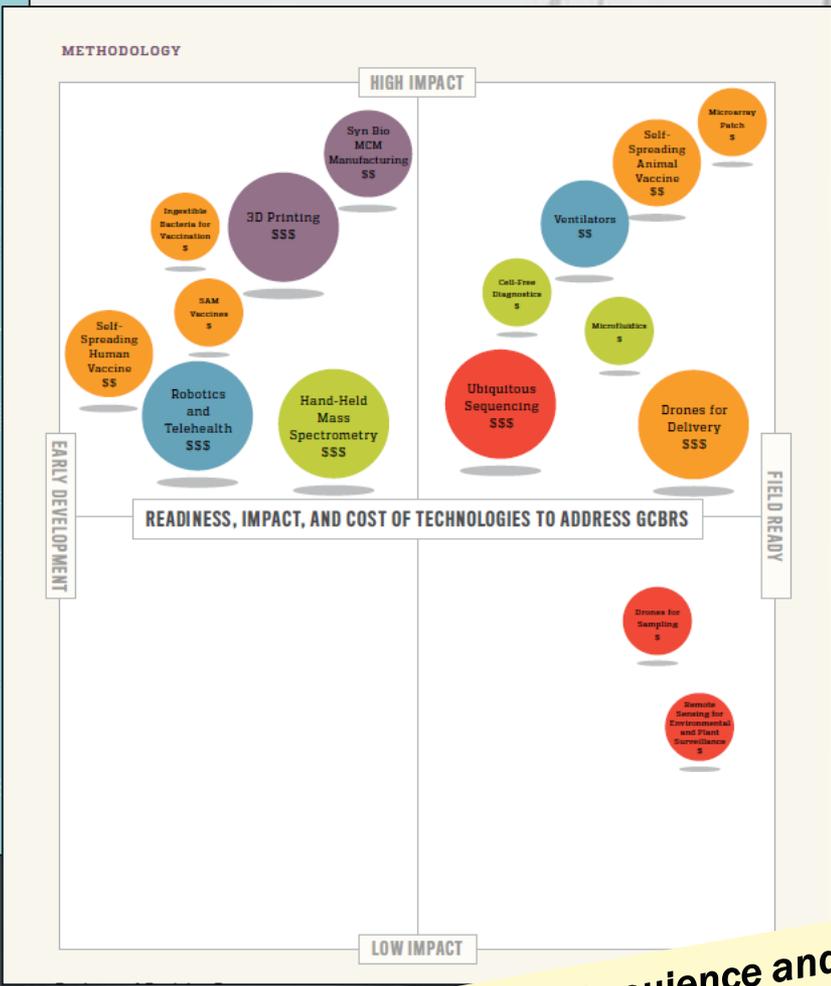
PRESS MENTIONS

Uncertainty...

What are the capabilities (independent of technology) we need?

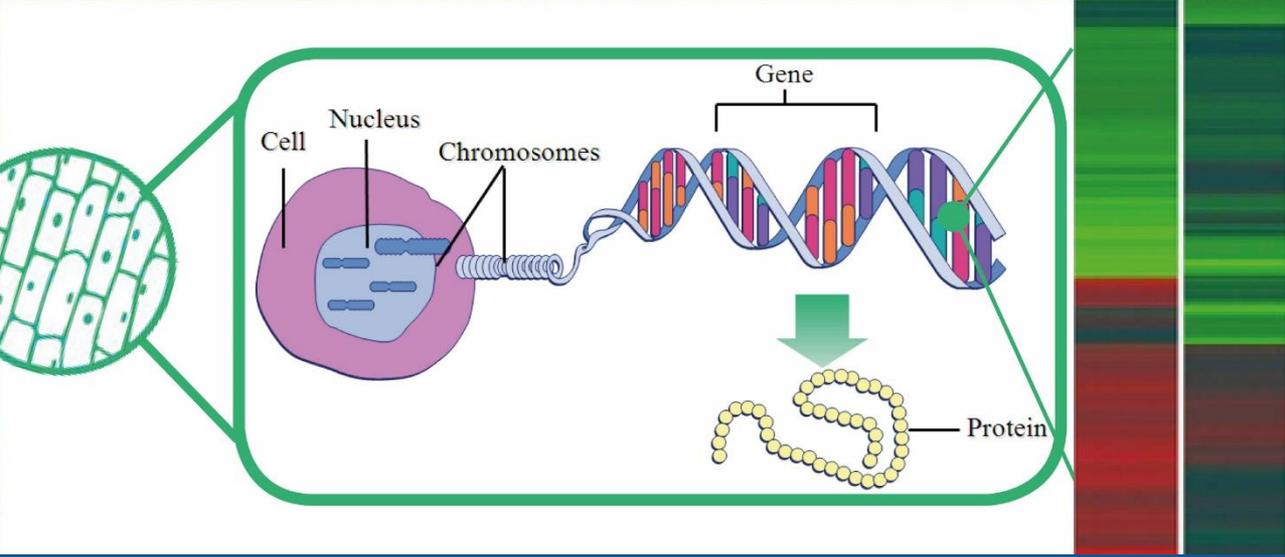
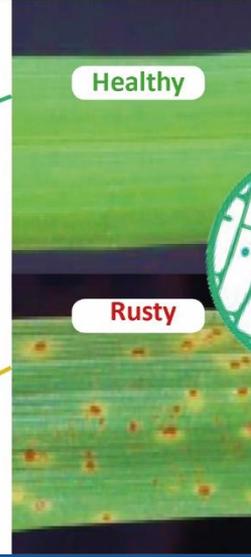
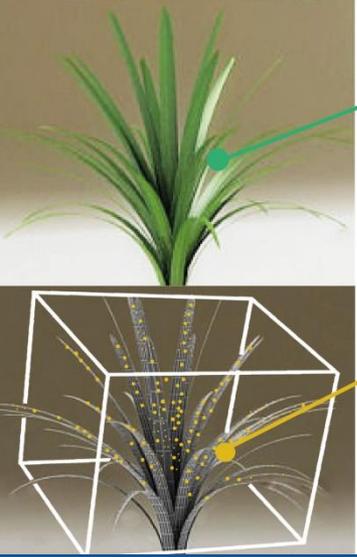
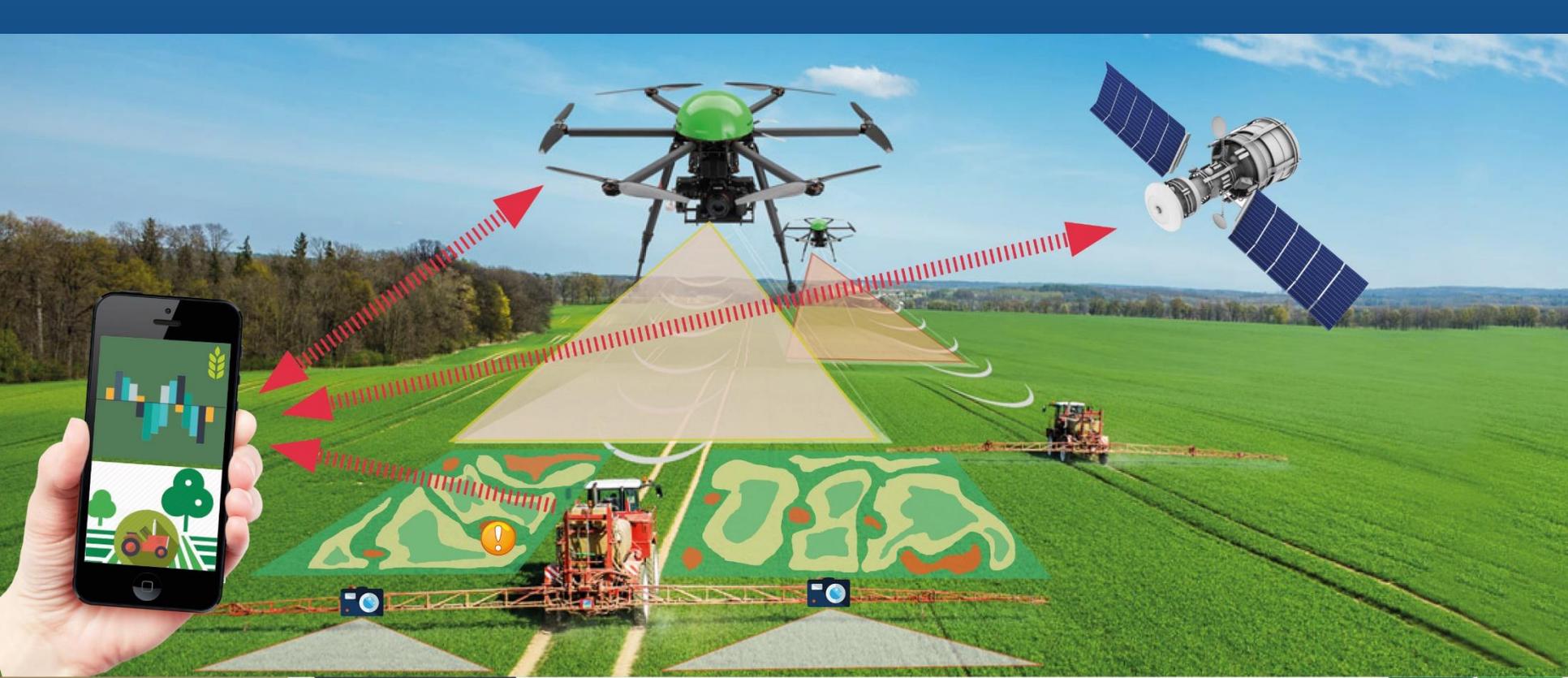
What Scenarios Do We Need to be Prepared for?





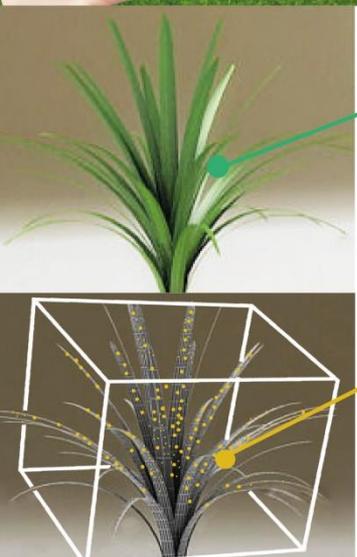
Once you answer these questions, you can talk about science and technology...
 New technology vs. old technology?
 What do we need? What works reliably?
Focus on needs and capability requirements

ident of
 ared for?



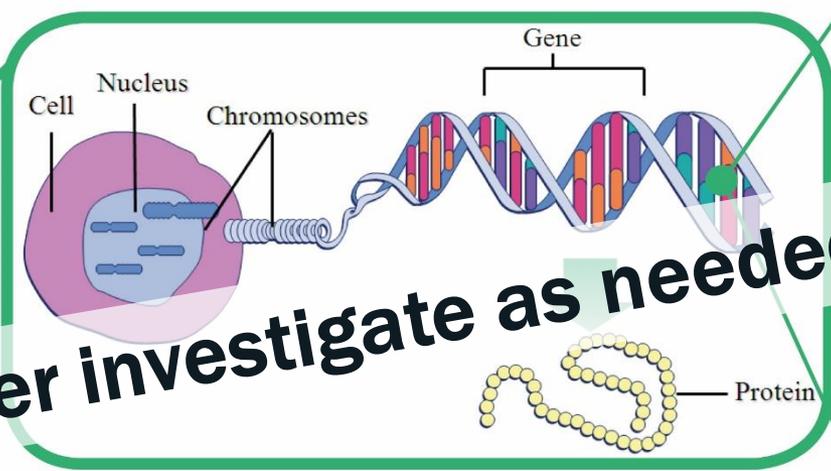
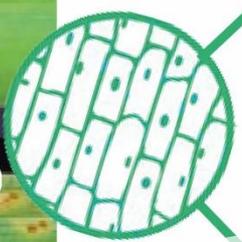


Recognize when something is "not right"



Healthy

Rusty



Further investigate as needed

Cell

Nucleus

Chromosomes

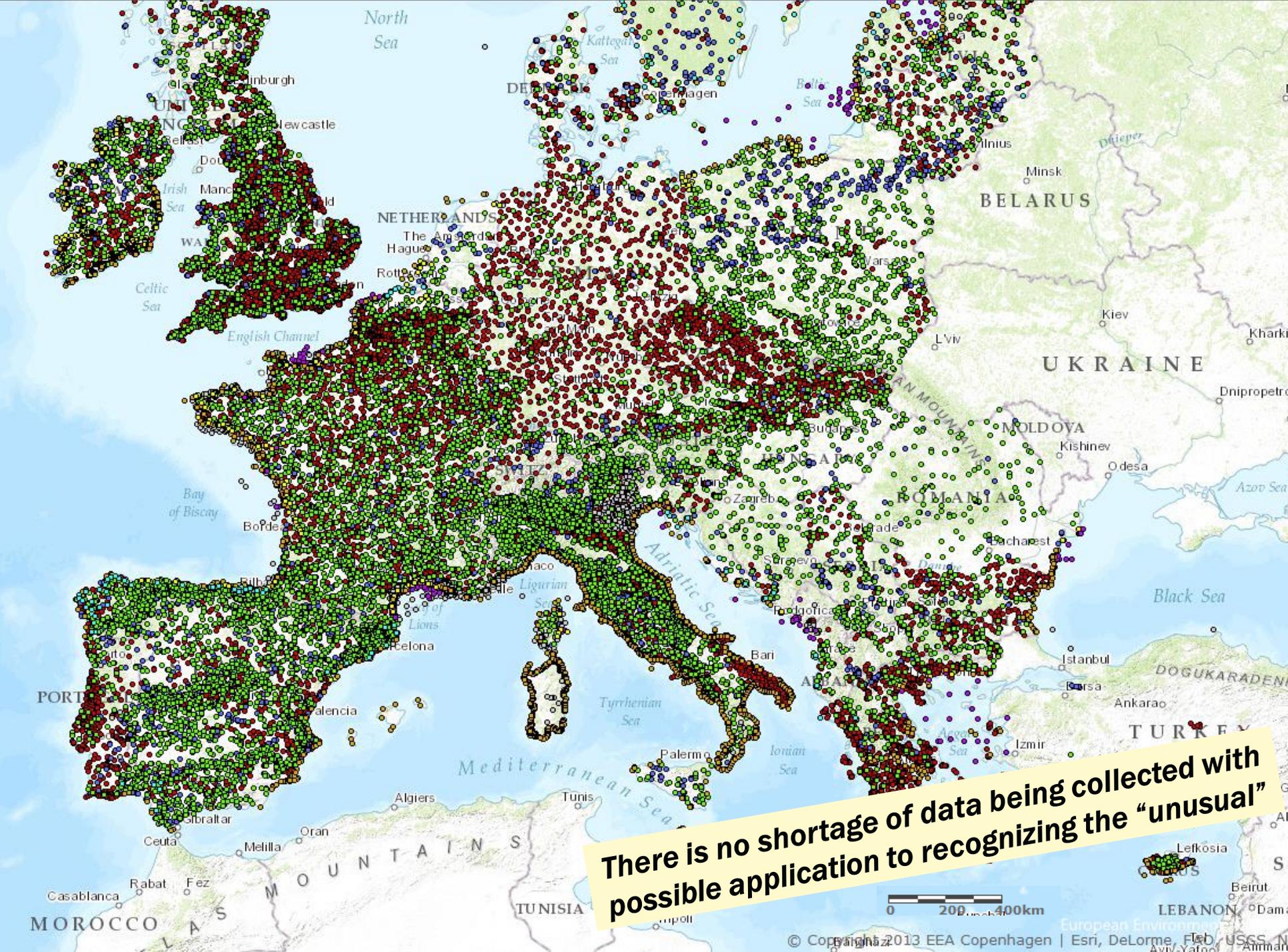
Gene

Protein

If Plants Could Talk...



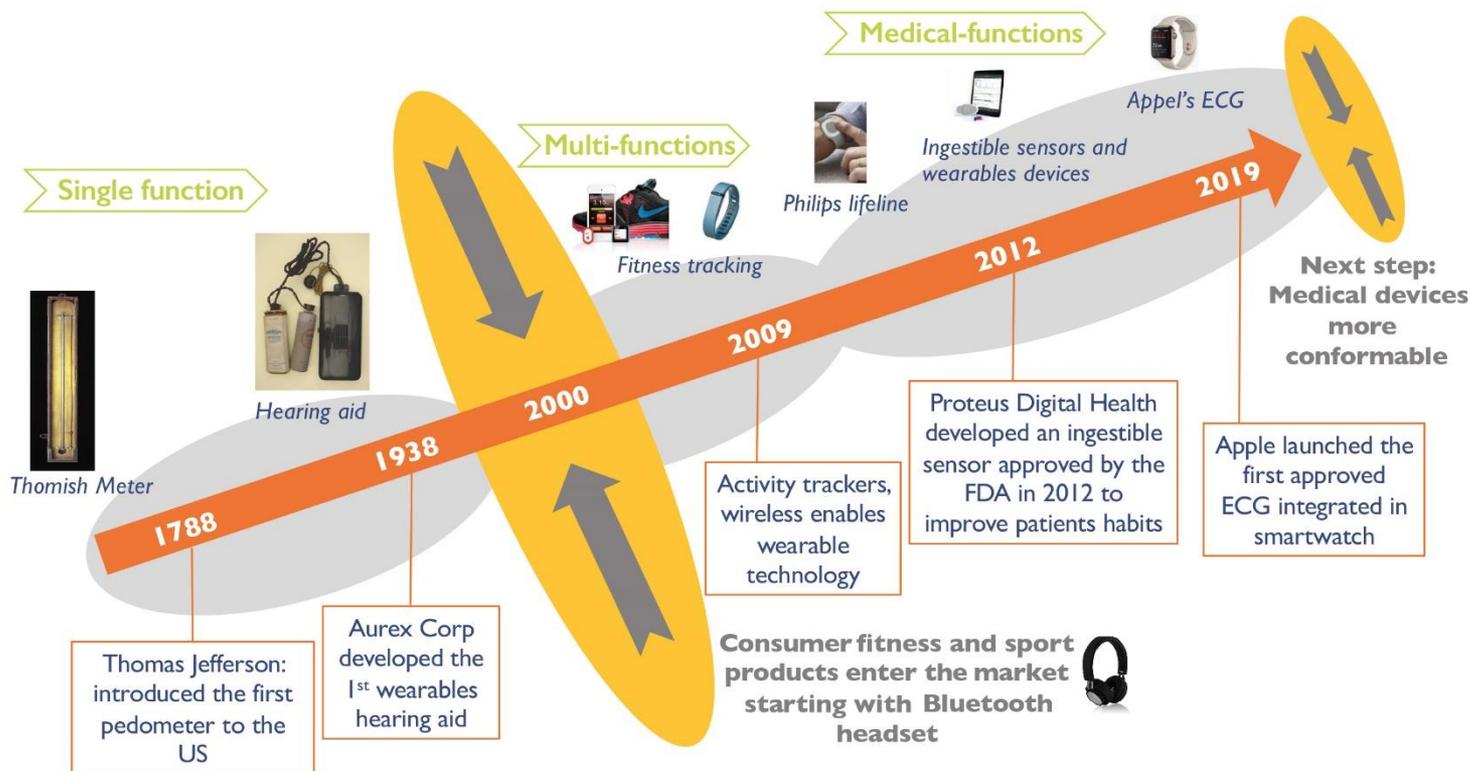
**“The signs are that the bombs were made with the windows open but the net curtains taped to the walls to avoid being seen. The fumes had killed off the tops of plants just outside the windows”
- Report of the Official Account of the Bombings in London on 7th July 2005**



There is no shortage of data being collected with possible application to recognizing the "unusual"

Timeline of wearables: a little bit of history

(Source: Medical Wearables: Market and Technology Trends 2019 report, Yole Développement, March 2019)



possible applications

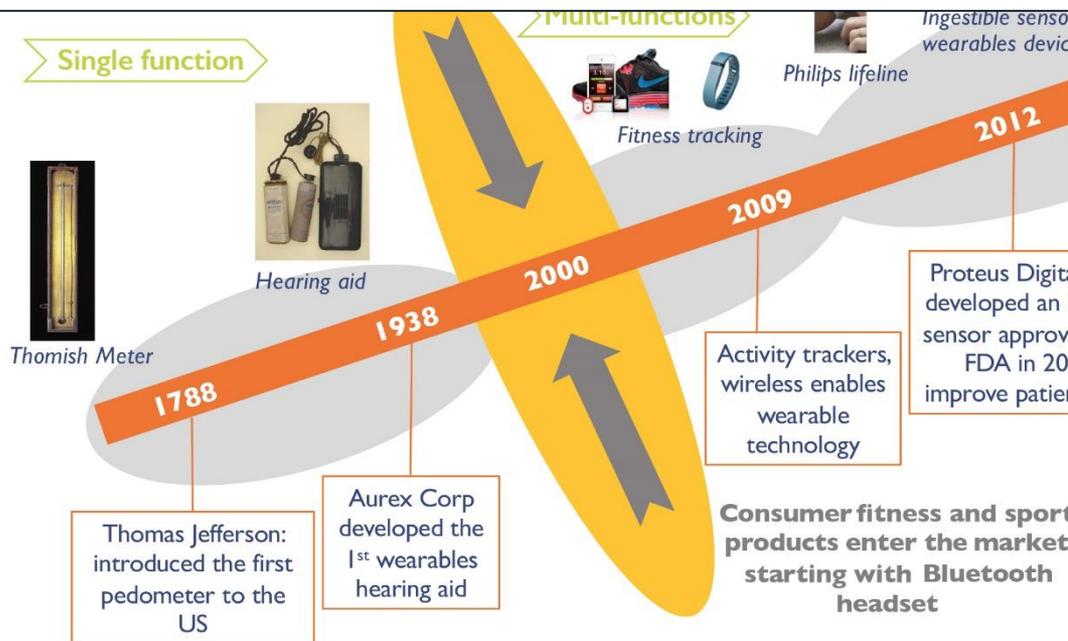


New technology gives early warning of exposure to disease-causing pathogens

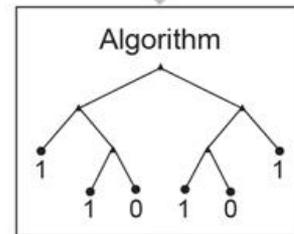
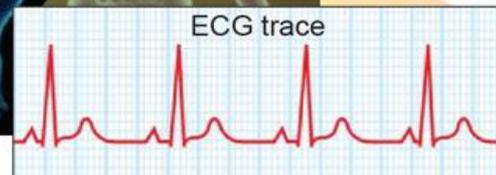
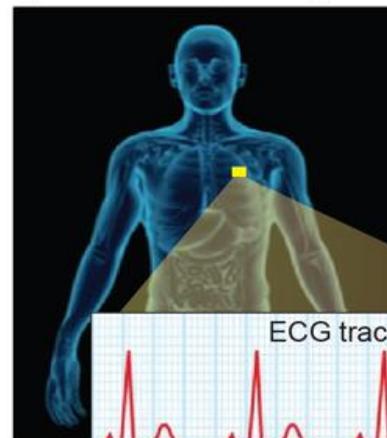
The enabling algorithm uses non-invasive physiological data to predict the probability of viral or bacterial exposures.



DECEMBER 5, 2017 | Dorothy Ryan | Communications & Community Outreach Office



Subject wears heart activity monitor



Result relayed to mobile device

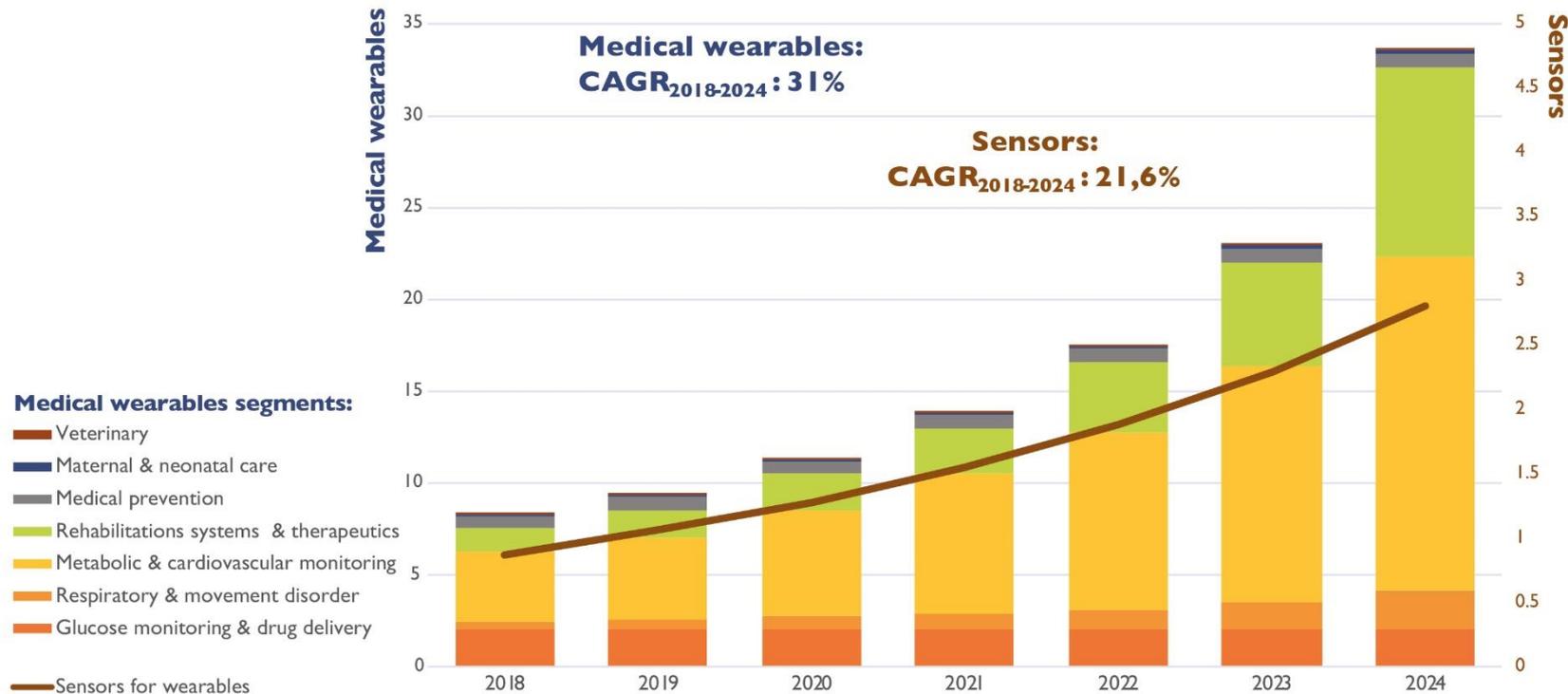


Yole Développement is part of Yole Group of Companies

possible applications

Medical wearables and sensors: 2018 – 2024 market forecast (in B\$)

(Source: Medical Wearables: Market and Technology Trends 2019 report, Yole Développement, March 2019)





Digitization transforms the Chemical Industry rapidly across its entire horizontal value chain



More efficient tracking of imports and exports?
Non-proliferation benefits?

**Big-data/
advanced
analytics in
OpEx/
CapEx:**

Big data-driven raw material analytics to optimize feedstock costs

**End to end
supply chain
integration:**

Production data sharing with suppliers/ real-time supply tracking

**Process
automation:**

Sensor-based production control and real-time optimization of YETQ¹

**Integrated lean
system:**

IT-based integrated lean system to drive manufacturing excellence

**Engineering/
R&D 4.0:**

Machine-learning-driven recipe and formulation improvements

**New roads to
market:**

Using online/marketplace sales channels

**Digitization
of customer
experience:**

Customer self-service platform

**Digital
procurement
tools:**

Digital tools enabling more efficient procurement processes

**Predictive
maintenance**

Advanced analytics-based predictive and risk-based maintenance

**Digital
manufacturing**

Production automation by application of autonomous logistics, drone inspections

**Risk
management:**

Advanced analytics-based risk management/cyber security

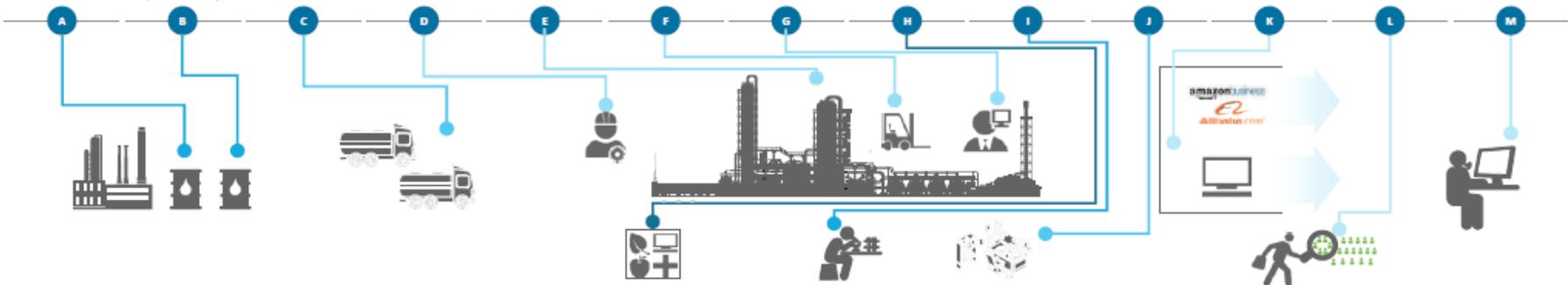
G&A 4.0:

Back office automation, e.g., no touch orders

**Commercial
engines:**

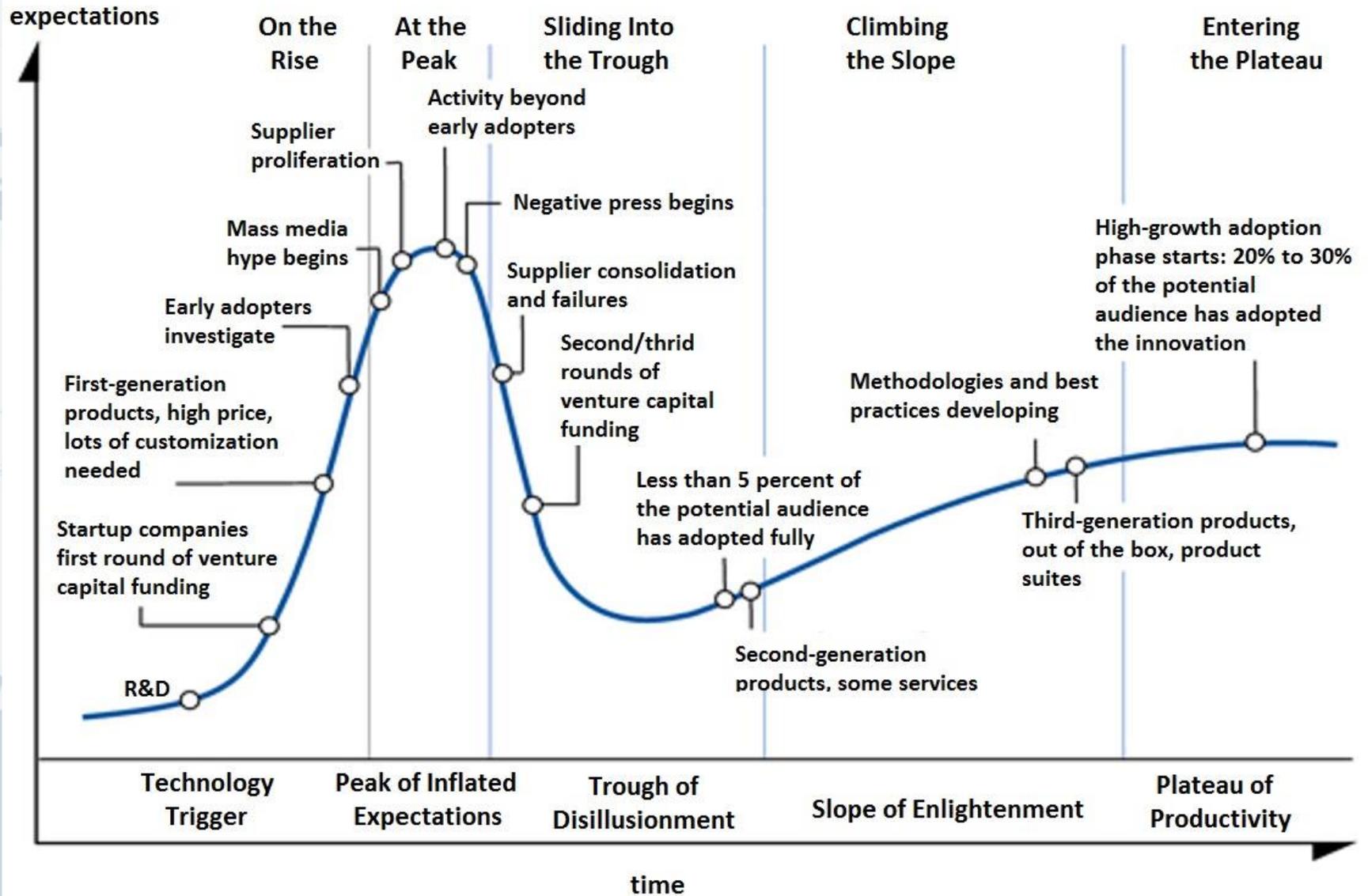
Use advanced analytics for lead generation, etc.

THE DIGITAL CHEMICAL COMPANY

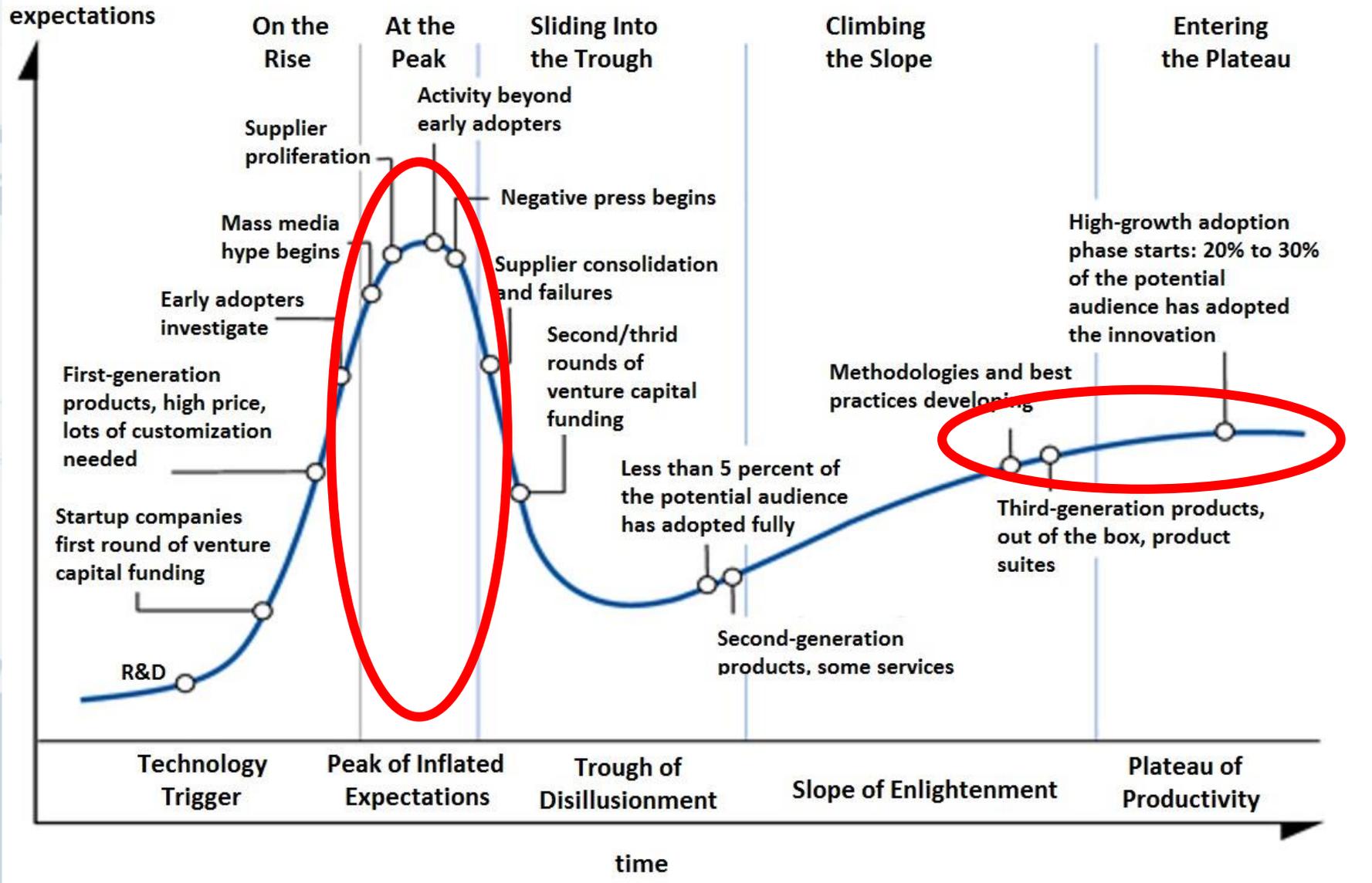


PLUS: new, radically different business models

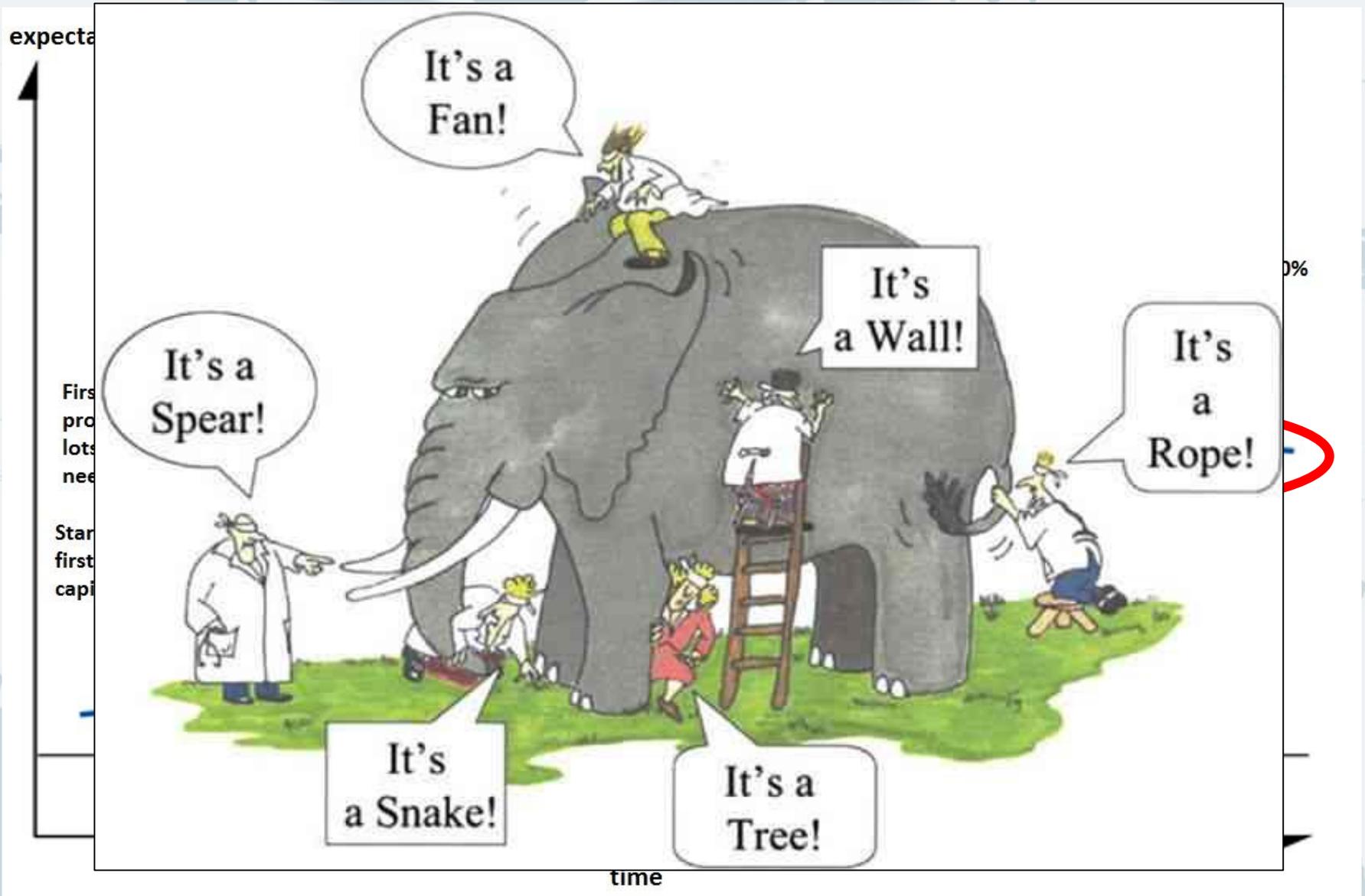
A Practical View of Science and Technology is Needed



A Practical View of Science and Technology is Needed

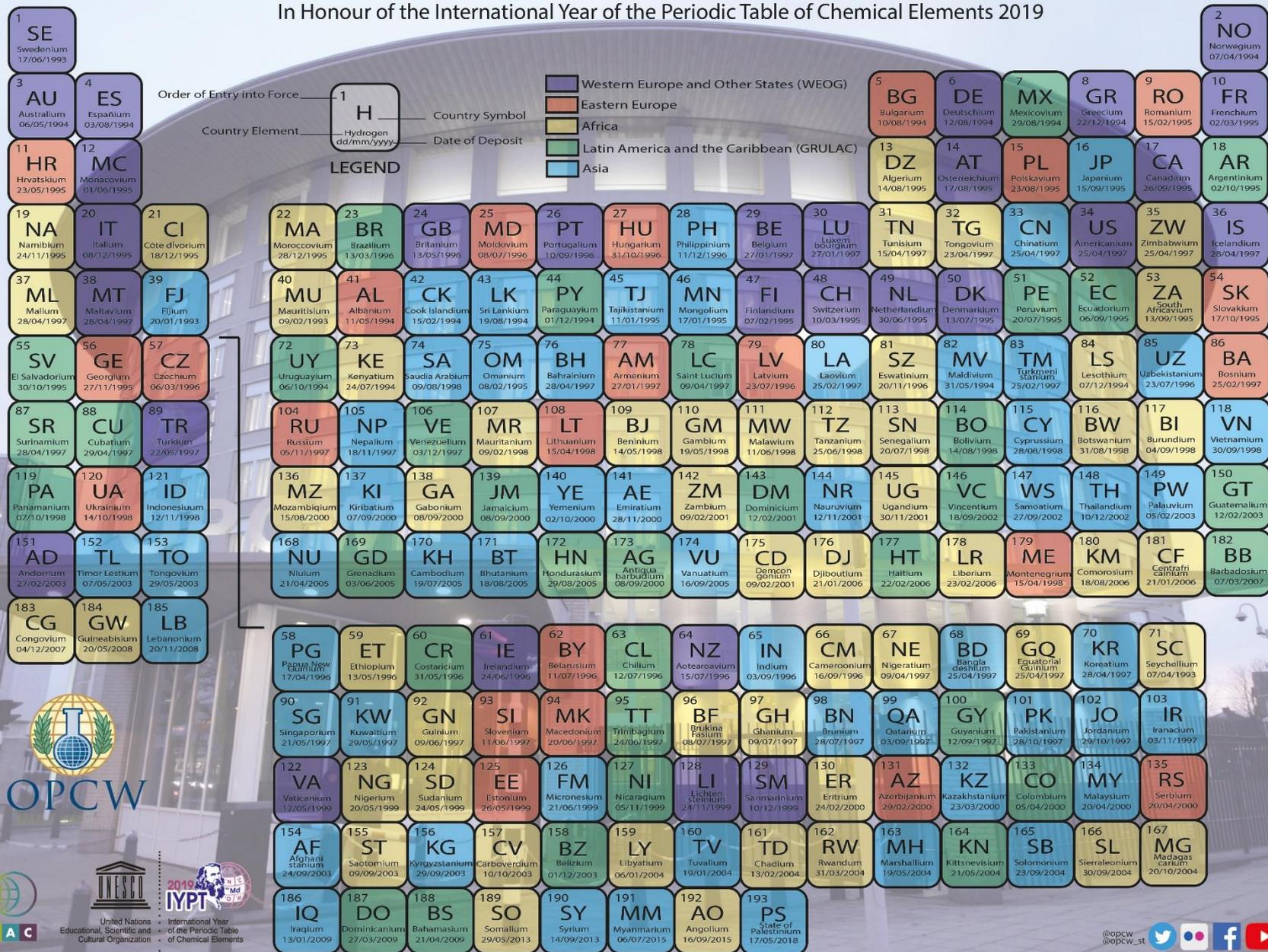


A Practical View of Science and Technology is Needed



Periodic Table of States Parties to the Chemical Weapons Convention

In Honour of the International Year of the Periodic Table of Chemical Elements 2019



United Nations Educational, Scientific and Cultural Organization

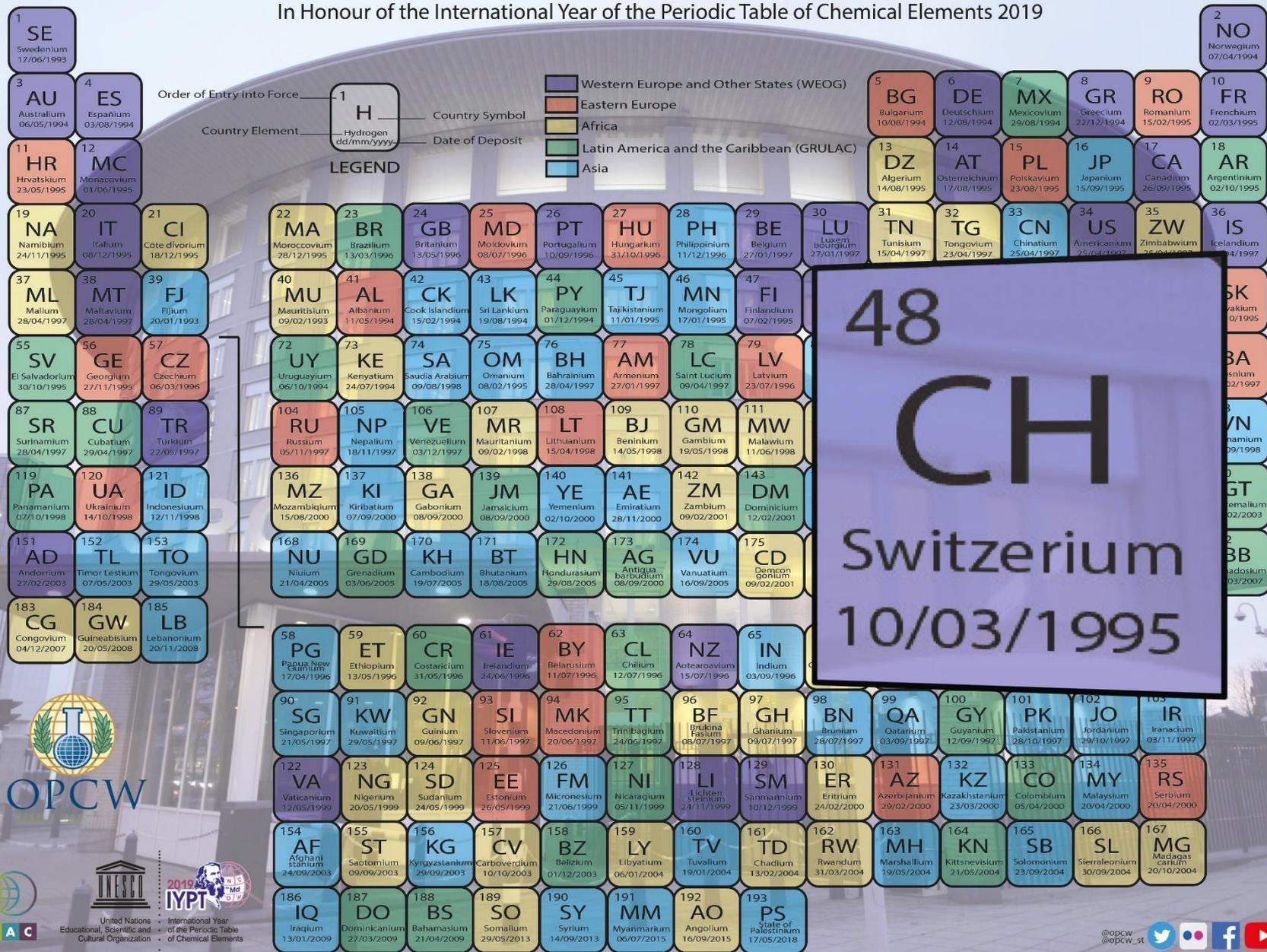


International Year of the Periodic Table of Chemical Elements



Periodic Table of States Parties to the Chemical Weapons Convention

In Honour of the International Year of the Periodic Table of Chemical Elements 2019



United Nations Educational, Scientific and Cultural Organization



International Year of the Periodic Table of Chemical Elements

Scientific and Technological Change

- **Uncertainty is the challenge!**
- **Technological change is inevitable**
- ***Disarmament non-proliferation cannot afford scientific illiteracy***
- **We Need Innovative ideas, approaches and policies**



OPCW



OPCW

منظمة حظر الأسلحة الكيميائية

禁止化学武器组织

Organisation for the Prohibition of Chemical Weapons

Organisation pour l'Interdiction des Armes Chimiques

Организация по запрещению химического оружия

Organización para la Prohibición de las Armas Químicas