Chemistry, Technology and Drug Discovery; A Personal Perspective

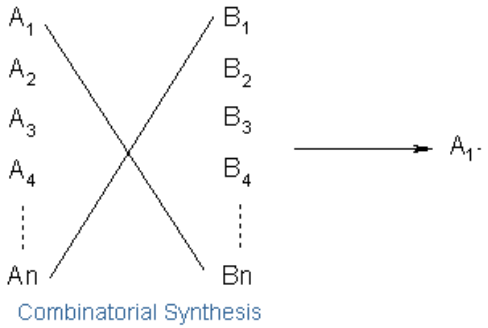
Martyn Deal; Radleys

High Throughput Chemistry – the beginning

Combinatorial Chemistry

The vision

- Early/Mid 1990's
- Synthesis of vast libraries of molecules (>10^6)
  - Combinatorial synthesis $R1_{100}$ x $R2_{100}$ x $R3_{100}$
  - based on automated peptide synthesis techniques (solid phase chemistry)



Combinatorial Synthesis

- Combined with HTS (high throughput screening)
- Provide rapid access to Drug Candidate Molecules from any biological target identified from uncovering the human genome.

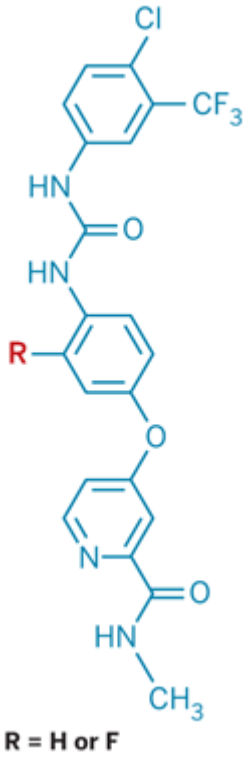
This would solve the Pharma Industry's problem:-
- discover **more** drugs **quicker**

The Reality

After 20 years - 1 drug on the market derived from Combinatorial Chemistry

Sorafenib

- Bayer/Onyx collaboration
- Raf kinase/VEGFR dual mode of action
- Approved in US, 2005, renal cell carcinoma
- Started from a lead structure from chemical library hit in high throughput screening



R = H or F

- Not a great return on investment in the technology!

- Most large pharma have now moved away from original concept of "combinatorial chemistry"

What Went Wrong?

- Lack of quality – chemistry (and biology) and choice of molecules
    - Emphasis on numbers
    - “What **can** we make?”
    - Not “What do we **need** to make?”

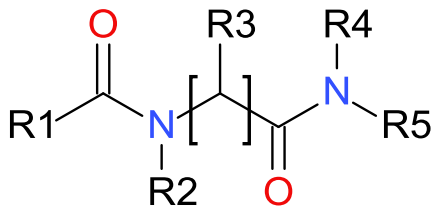
- Lack of hardware
    - Technologies for synthesis and purification not properly developed

- Lack of diversity
    - Initially no ways to measure it

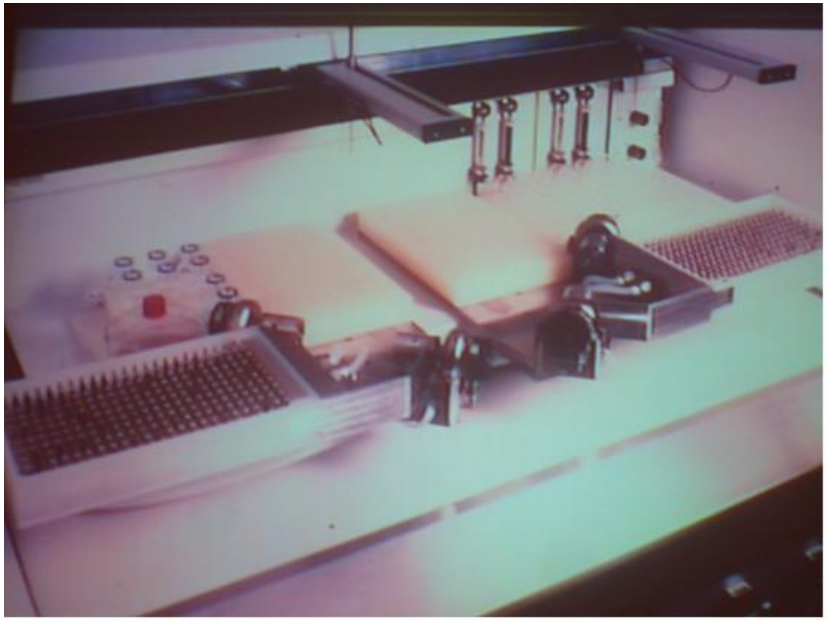
- Lack of QA
    - Technologies not available

- Too much belief that **automation** was the answer

GL1



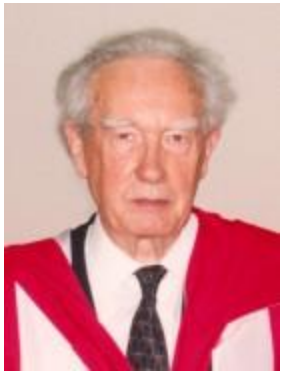
160 000 diamides
Mixtures of 40 compounds
QC by HPLC only



ARNIE

First custom built automated synthesiser

Sir Derek Barton



“Are you sure you want to be doing this? ”

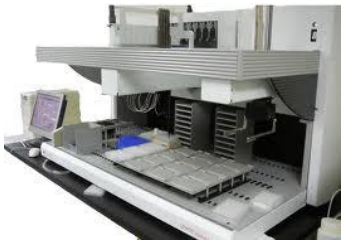
Automation - where does it fit?

Best suited for high repeatability tasks

- Successfully employed in Biological high throughput screening applications where these processes are fundamental.

- **Not** Diverse operations of chemistry with aggressive/corrosive chemicals

- Only really fits for liquid handling applications
  - Adding solvents/reagents
  - Sampling for analysis
  - Plate transfers



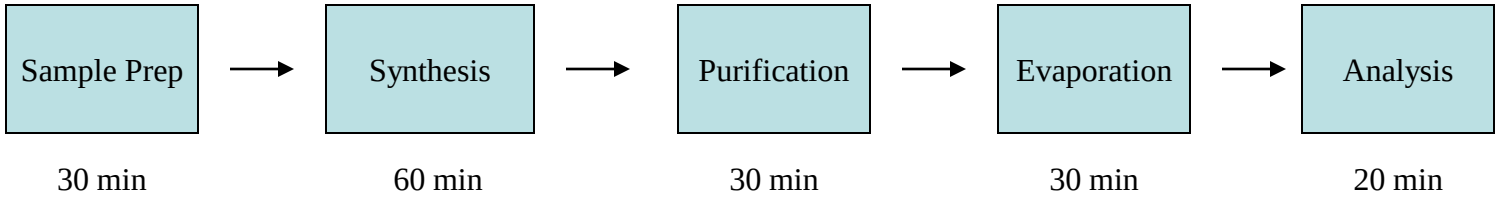
- Also successfully employed moving contained samples in and out of processes

Some Pitfalls of Automation

- Full integration can limit flexibility – need modularity

- Automating/Integrating a full process can be time inefficient, with high hardware redundancy.

Typical Chemistry Process



- Eg Synthesis hardware only utilised for 60/170mins – 65% redundancy
- Aim to **parallel** operations where possible
- Scheduling software essential to manage the process

- Clear requirement for robust tried and trusted hardware and integration links. If one part breaks, its all broken

Automation and Diversity

Mass produced objects made by a single process

A diverse set made by one process with variation.

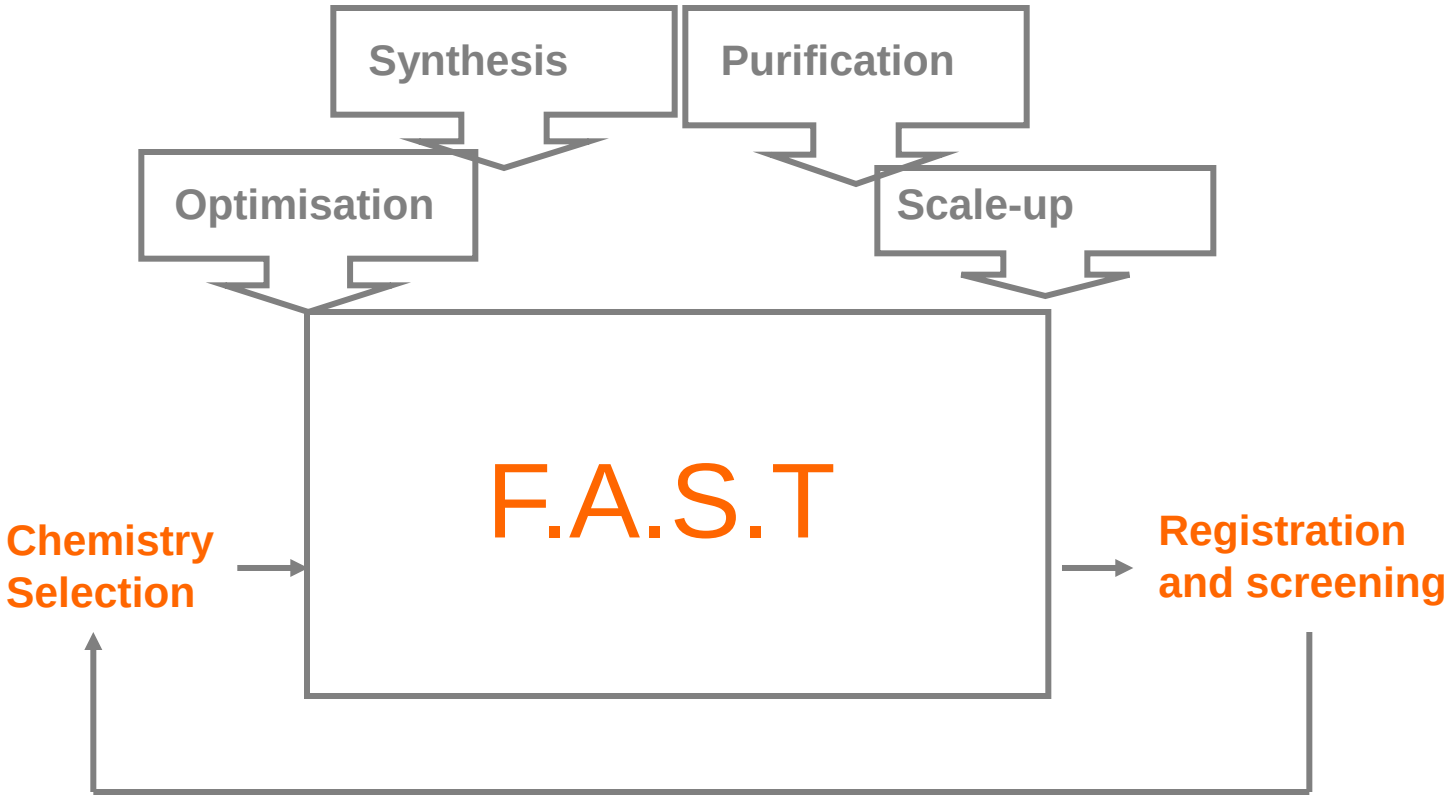
A set of diverse sets made by different processes.

A diverse set collected over time from different processes

What is Really Needed:- Fast Iteration

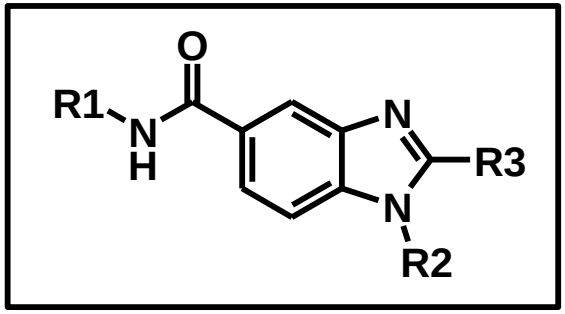
Drug Discovery Cycle:-

- Choose the Molecule (s)
- Make It (Them)
- Get (and interpret) the result (s)
- Do it in parallel and do it fast!

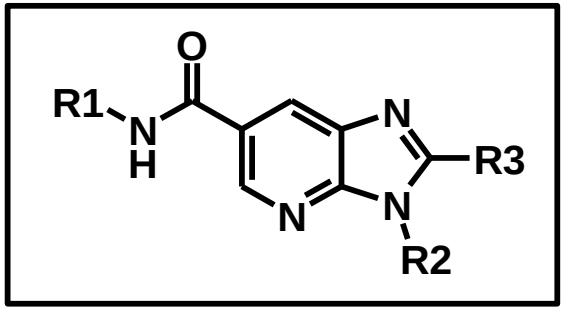


Evolution to Parallel Synthesis

Better understanding of diversity
Move to smaller focused libraries

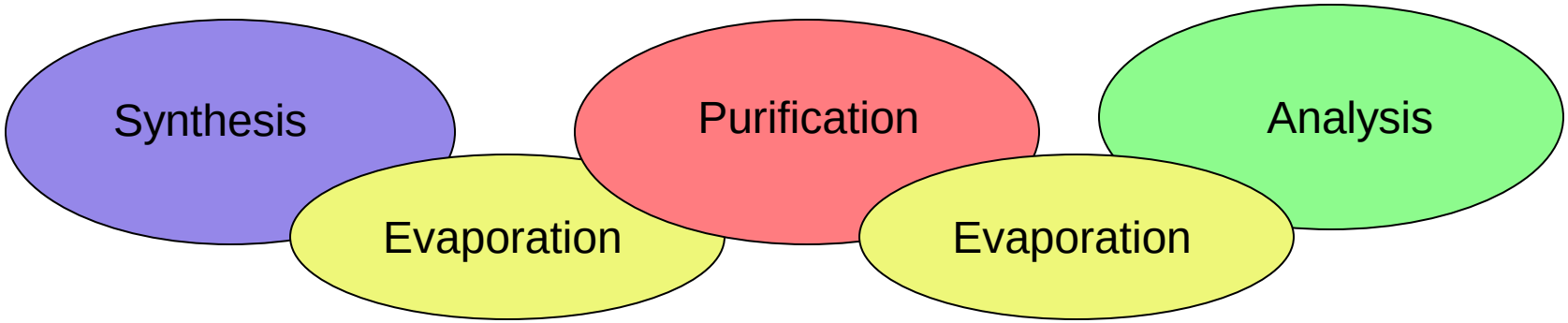


Diversity **around** a central core



Diversity **of** the central core

Development of hardware for the key processes



Synthesis

Requirements

- Heat/cool multiple reactions
- Stirring, Reflux, Inert Atmosphere
- Perform full range of chemistries

Evaporation

Requirements

- Remove synthesis solvents
- Remove purification solvents

Purification

Requirements

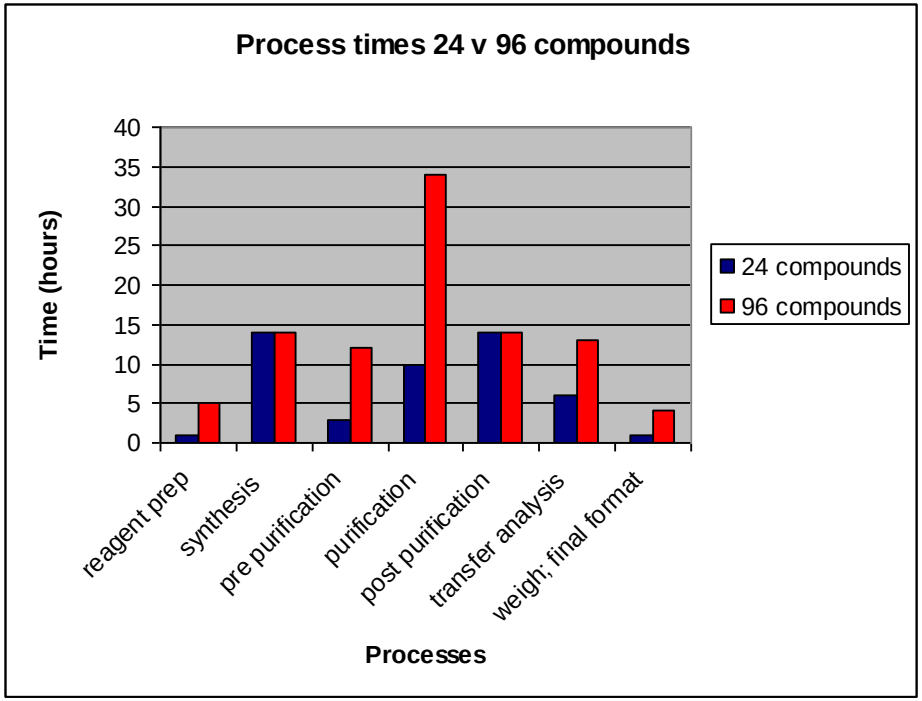
- Separate required product from unwanted impurities
  - Solid/Liquid phase separation- filtration, chromatography
  - Liquid/Liquid phase separation

- Development of analytical tools LCMS
- Development of purification tools MDAP

Review of findings from literature

- Parallel synthesis provides more information per cycle than individual compound synthesis
- Overall cycle time must not be impacted by increase in numbers
- Success is critically dependent on speed of each part of the iterative cycle (no bottlenecks)

- Cycle time for some steps highly dependent on numbers

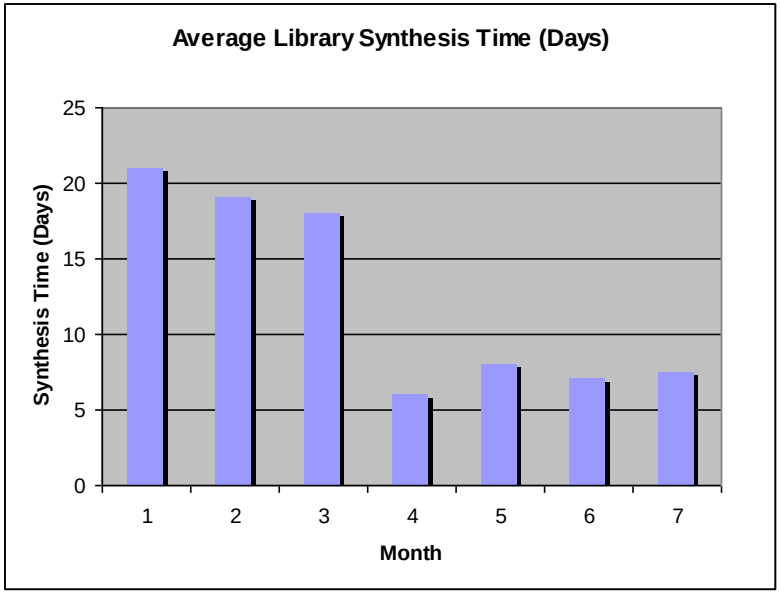


Application of Lean Manufacturing Concepts to Drug discovery: Rapid Analogue Library Synthesis
Harold Weller et al; BMS; J. Comb. Chem; 2006; 8; 664-669

Review of findings from literature continued…

Process optimised over time

- Reduced maximum library size to 48 compounds
- Streamlined reagent/building block supply
- Eliminated “non value added” steps
- Library tracking/planning



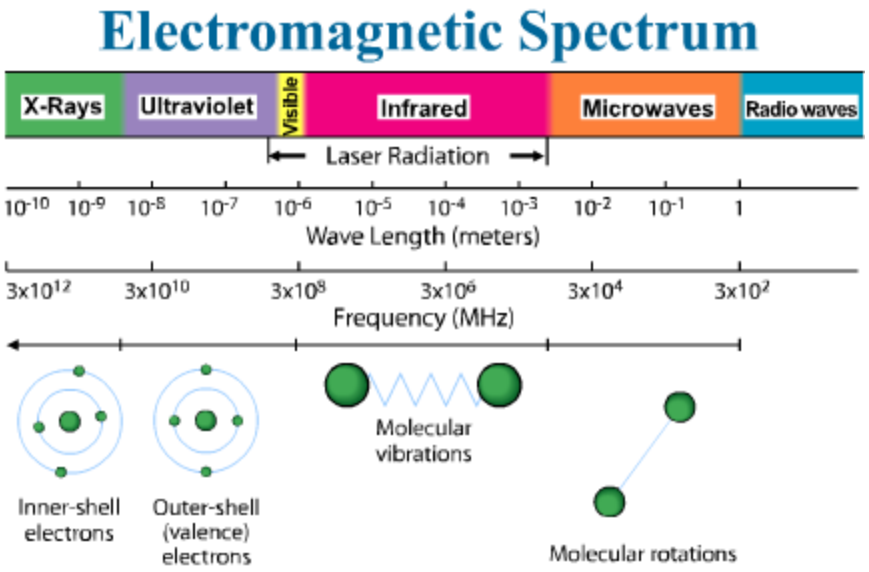
- Library (48 compounds) cycle time reduced from 21 days to 7 days

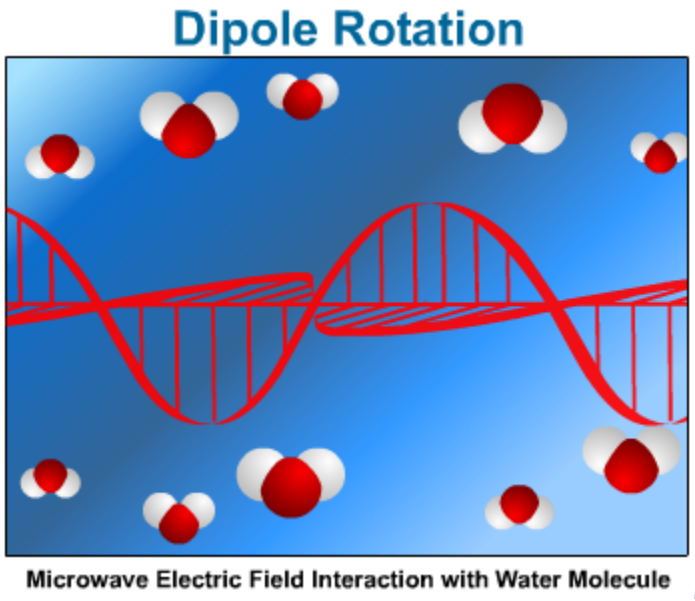
Application of Lean Manufacturing Concepts to Drug discovery: Rapid Analogue Library Synthesis
Harold Weller et al; BMS; J. Comb. Chem; 2006; 8; 664-669

Further Reading

Factors Determining the selection of Organic Reactions by Medicinal Chemists and the use of these reactions in arrays (Small Focussed Libraries); A.W Cooper; IB Campbell; S. Macdonald; Angewande Chemie;49;8082-8091 2010

Microwave Synthesis



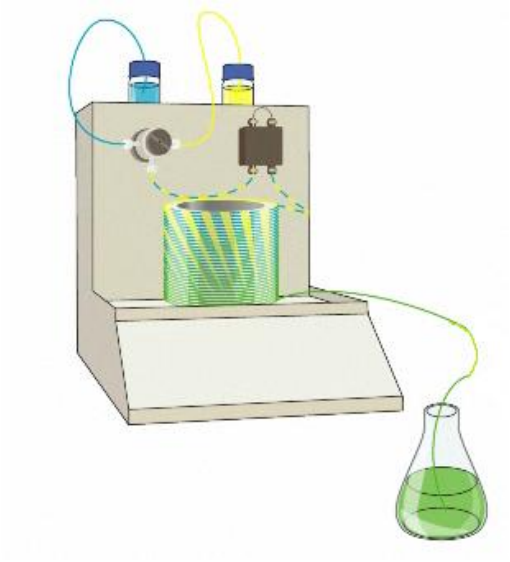


Microwave Electric Field Interaction with Water Molecule

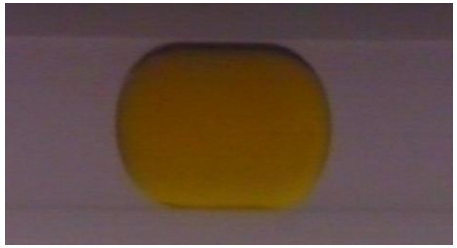
- Localised High Energy Activation
- Forcing conditions - Pressure, Superheated solvents
- Access to New Chemical Space

A positive impact on drug discovery

Continuous Flow Synthesis



Continuous Flow

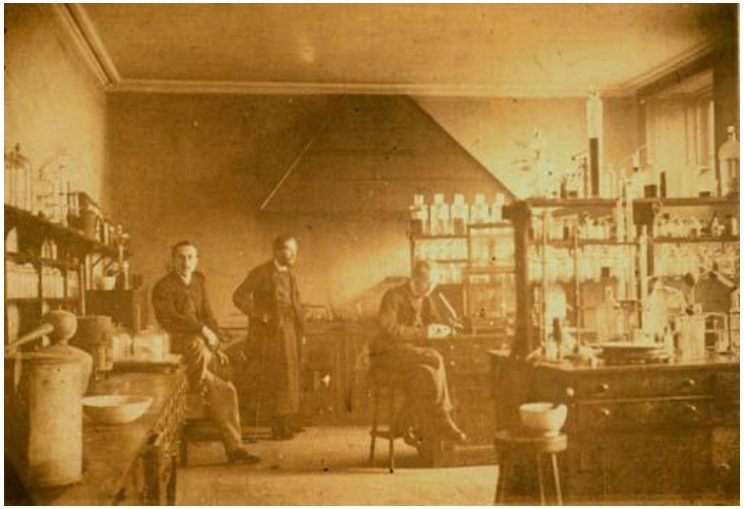


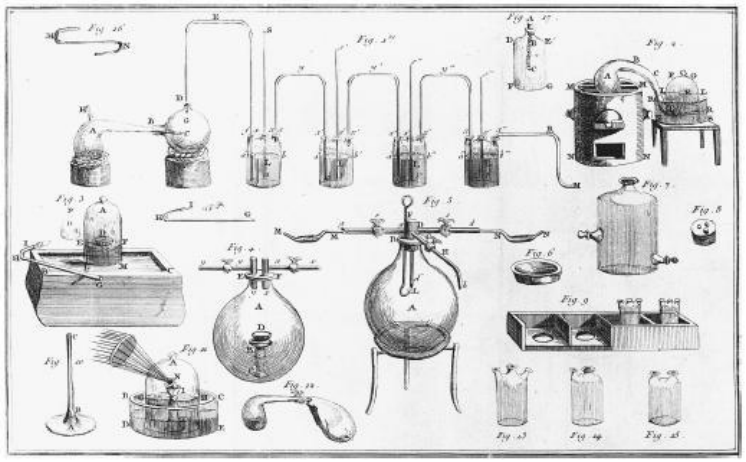
Plug Flow

- Hazardous species
- Short lived intermediates
- Access to new chemical space

A positive impact on drug discovery

1900

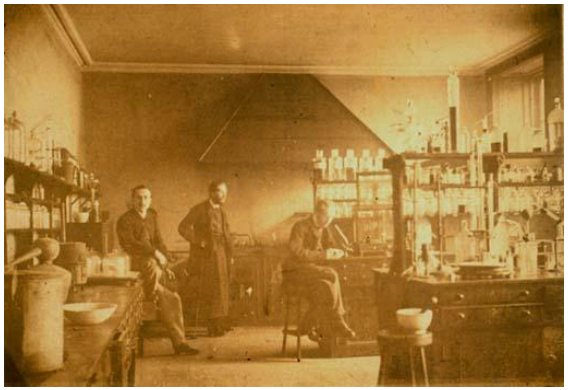


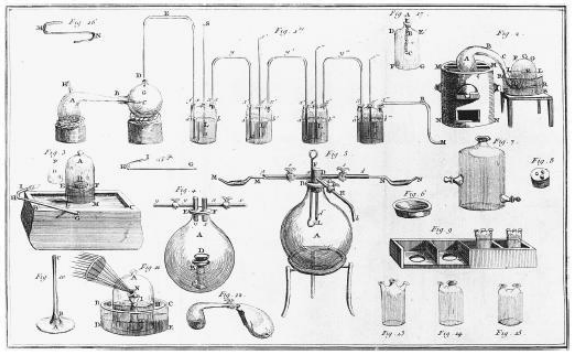


Wouldn't it be great if we could ..

- Have a machine that got all our reactions to happen in 10 minutes
- Have a machine to separate all the components of our reaction in 20 minutes
- Have a machine to tell us the molecular weight of our product (and all the impurities) in 5 minutes
  - and another one to show us the molecular structure in 5 minutes
- Have instant access to any journal in the world without getting up from my desk

1900





2000

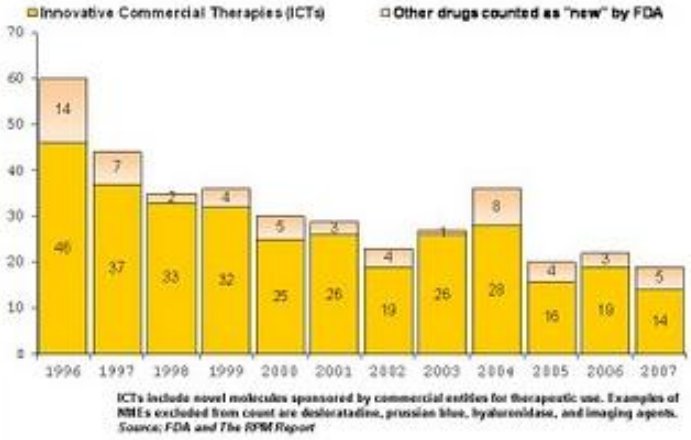
The Last 20 Years

- New Tools
- New Technologies
- Access to new Chemical Space
- Significant Increase in Analytical Capabilities
- Automation
- Computer Software for everything

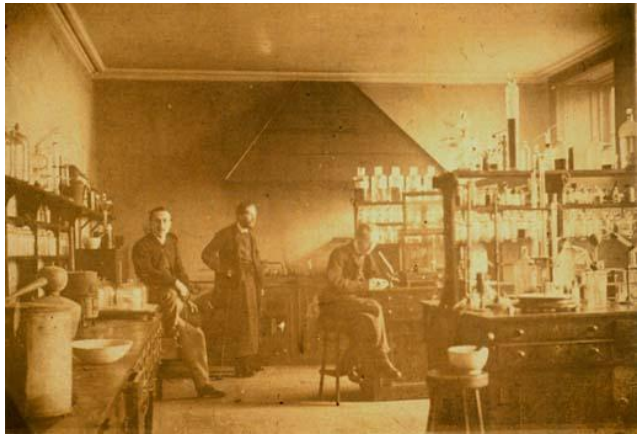
Working Practices in the chemistry lab **have** changed
Chemistry Cycle **is** Faster
Chemists **have** (infinitely) more information at their Finger Tips

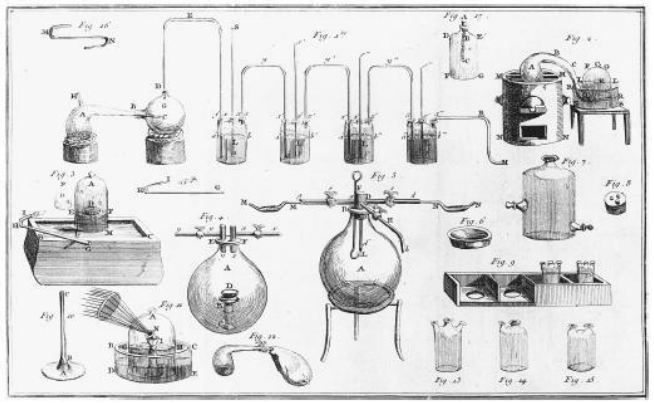
But Still the Success of Drug Discovery has failed to Improve!

Is Chemistry (or the way chemistry is done) Really the Issue?



1900





2000

2100

A Look to the Future

What will the Chemistry Lab be Like in **2100?**

Continued Evolution of Current Technologies
- how much further is there to go?

Or

A Quantum Leap

Wouldn't it be nice if …….

Ignore the boundaries and laws of physics and nature as we know them today – they are bound to be different in 100 years time!

What do we really need to make drug discovery more effective?

Nanotechnology

Going to Extremes

Visualise, Manipulate and Synthesise Single Molecules

Annu. Rev. Phys. Chem. 2003. 54:307–30
doi: 10.1146/annurev.physchem.54.011002.103852

First published online as a Review in Advance on February 27, 2003

STM Control of Chemical Reactions: Single-Molecule Synthesis

Saw-Wai Hla[1] and Karl-Heinz Rieder[2]
[1]*Department of Physics and Astronomy, Nanoscale and Quantum Phenomena Institute, Ohio University, Athens, Ohio 45701; email: hla@helios.phy.ohiou.edu*
[2]*Institut für Experimentalphysik, Freie Universität Berlin, D-14195 Berlin, Germany;*

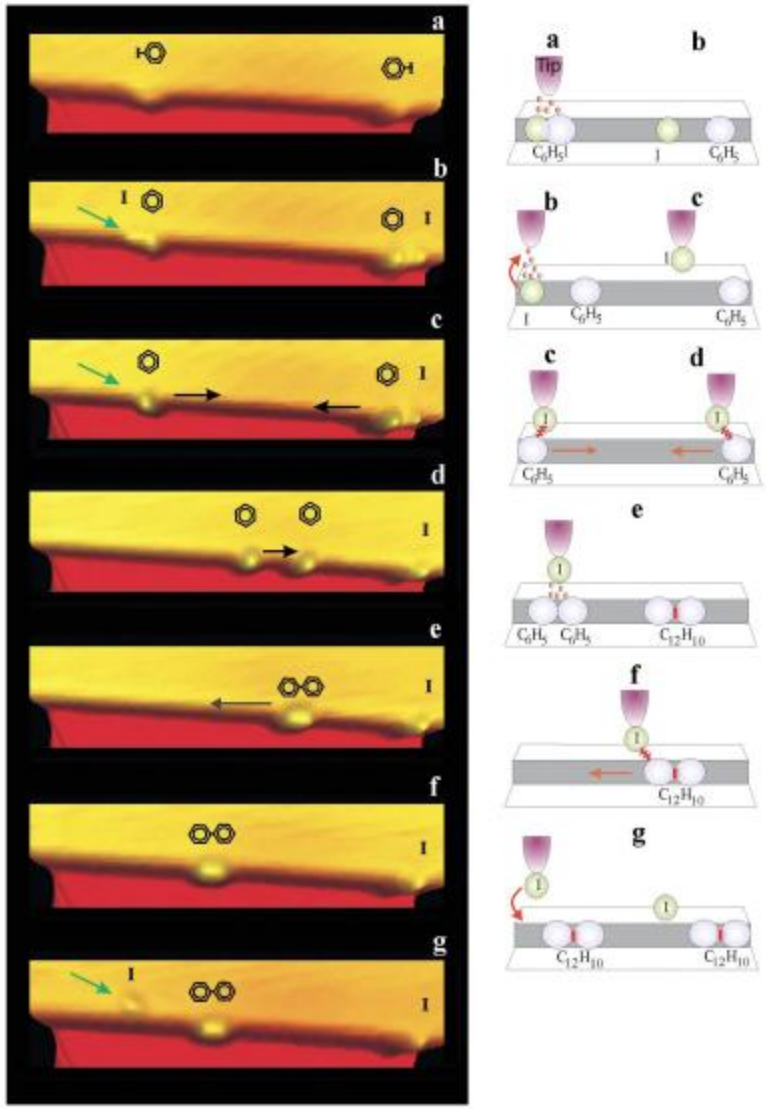
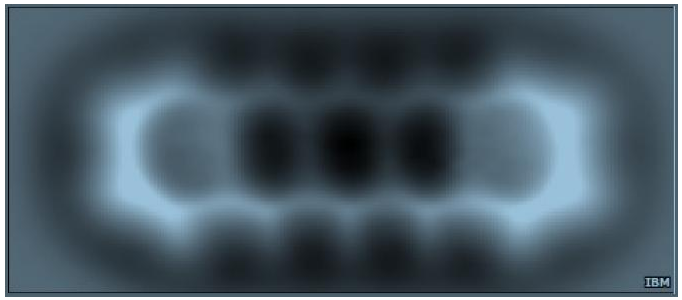


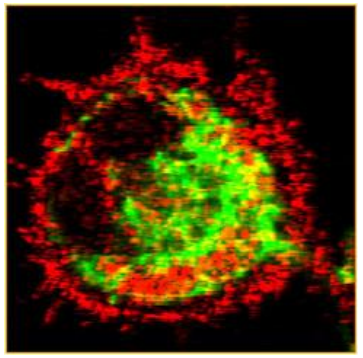
Figure 20 Single molecule Ullmann reaction series II: Two iodobenzene molecules are adsorbed at a Cu(111) step (*a*). After dissociation with tunneling electrons, two phenyl radicals (larger bumps) and two iodine atoms are adsorbed at the Cu step-edge (*b*). After the iodine at the far left (indicated by a green arrow) has been transferred to the tip apex using the vertical manipulation procedure, the image contrast improves (*c*). The two phenyls are laterally moved towards each other with the tip (*d*). When the two phenyls are in closest distance, a splash of electrons with 500 meV is supplied to excite them for biphenyl formation (*e*). Then, the synthesized biphenyl is pulled by the tip to the left side of the image to verify a successful chemical association (*f*). Finally, the iodine from the tip-apex is transferred back to the substrate (*g*) (indicated by a green arrow).

High Quality Imaging

- The more you see, the more you understand

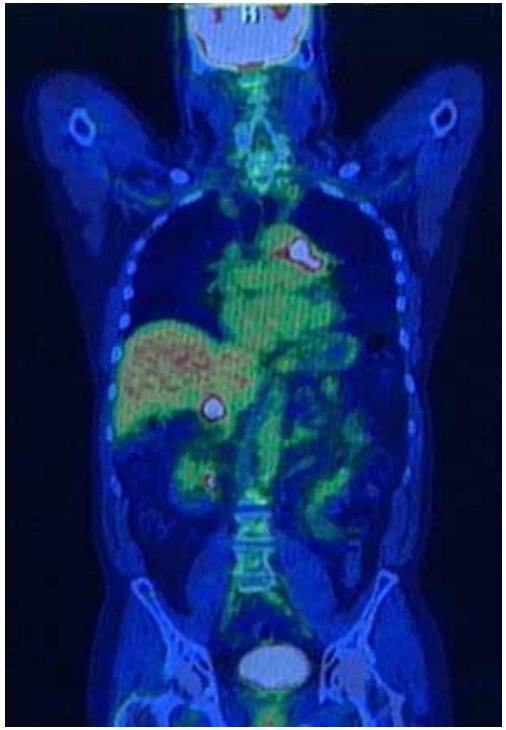


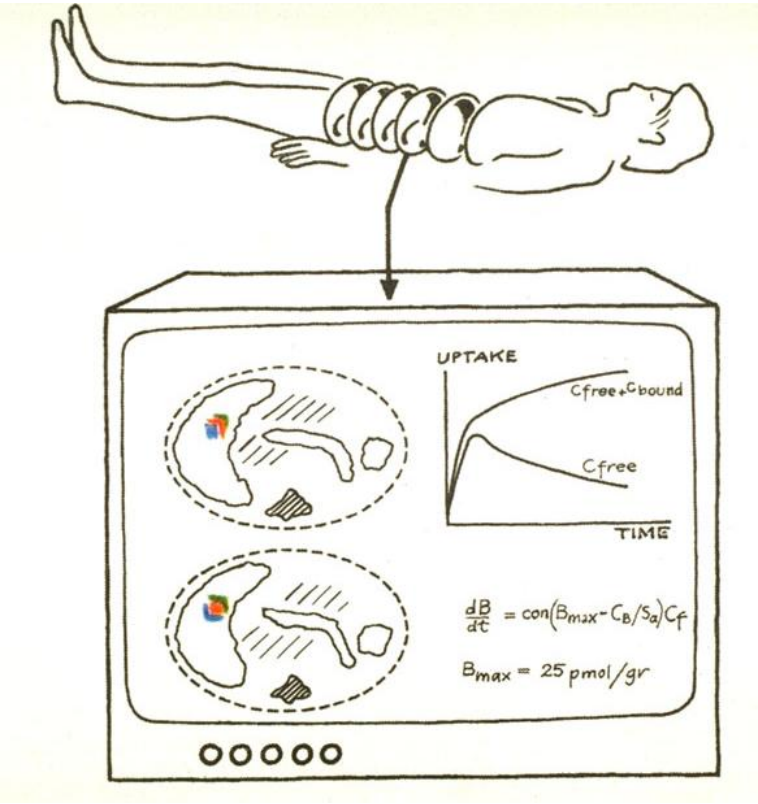
- The Chemical Structure of a single molecule (Pentacene) is imaged for the first time. *Science; Aug 2009*



- Single Cell Image by MPM (multiphoton microscopy)

High Quality Imaging



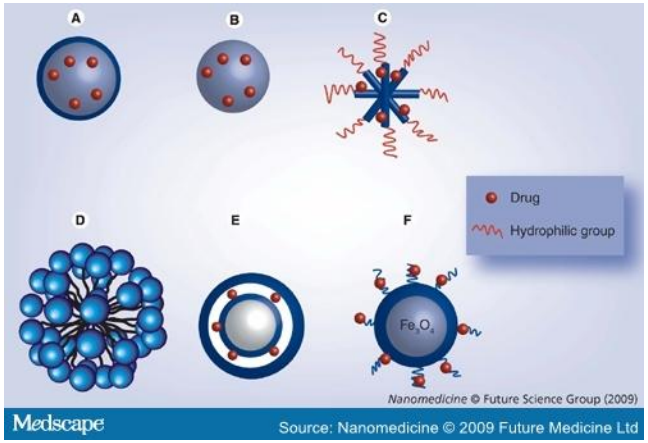


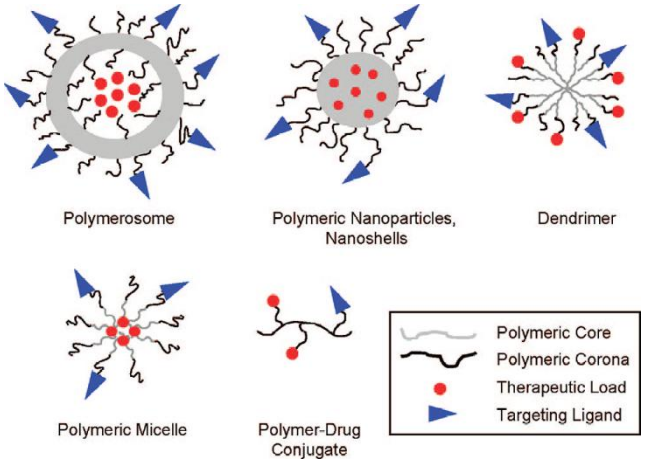
- PET imaging is current Gold Standard
- Track and trace with Radiopharmaceuticals and Radioligands
- Image individual molecules and their interactions in individual cells

Nanoparticles

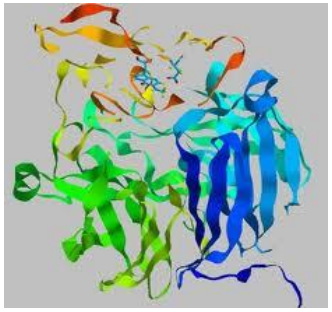
Custom designed particles

- drug delivery devices
- holding bioactive molecules
- functionalised surface to guide it through the body to required site
- controlled release of active material



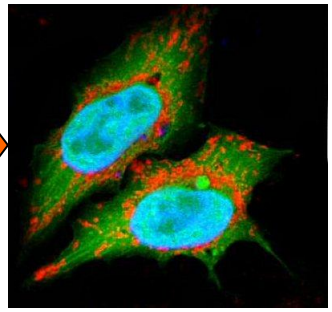


The Screening Cascade

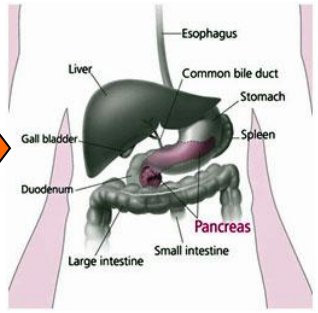


In Silico

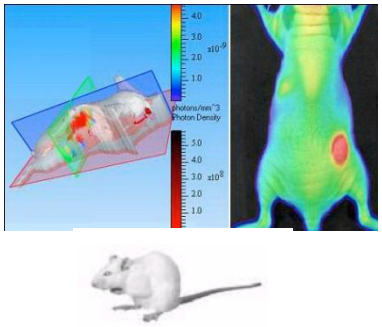
In Vitro



Cells

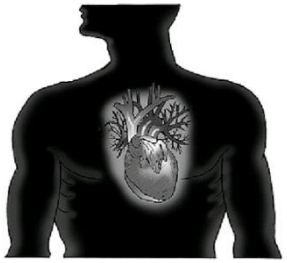


Organ



Small animal

Large Animal



Human

- **Not surprising that there's such a big failure rate!**
- **Is the Gap too big?**

Ultimate goal:- Primary Screening straight into Patient

How low does the dose need to be to be not harmful?

Single particle, containing a few molecules

High quality imaging to track and identify biological outcome

Summary

- Aim for the moon, but usually more useful things come out along the way
- Don’t be limited by “current knowledge” boundaries for long term projects
- Be prepared for “2 steps forward 1 step back”
- Need a multidisciplinary, integrated, quantum leap to really change things

Thank You