Diversity-oriented synthesis
- deliberate preparation of complex compound "libraries"
  for identifying drug leads

Solid-phase synthesis - we can prepare complex organic molecules attached to solid supports ("beads")

These beads look like little grains of sand
BACKGROUND FOR DISCUSSION OF COMBINATORIAL CHEMISTRY

SOLID PHASE SYNTHESIS - Chemical construction of a desired molecule proceeds via elaboration of a starting material that is covalently attached to an insoluble solid support like polystyrene or glass beads. This approach greatly facilitates isolation and purification because reagents used in synthesis can be washed away by filtration.

First developed by Merrifield for peptides and Letsinger for DNA. Now commonly used for the synthesis of many different types of molecules.
Polystyrene solid support prepared by polymerization of

\[
\begin{align*}
\text{Polystyrene solid support} & \quad + \quad \text{Polystyrene solid support} \\
& \quad + \quad \text{Polystyrene solid support}
\end{align*}
\]

1-2% 1%
Solid phase peptide synthesis involves repeated cycles of reactions:

\[ \text{Repeat cycle} \]

Yields must be high for each cycle. Overall yield = \((\text{percent yield})^x\) where \(x\) is the number amino acid cycles. 

E.g. 90% yield for each cycle, 5 cycles 

\[ 0.9^5 = 59\% \text{ overall yield} \]

If yield per cycle is 70%, overall for 5 cycles would be 17.4%
Key step in solid-phase peptide synthesis: DCC coupling

DCC = dicyclohexyl carbodiimide
H = Histidine

V = Valine

S = Serine

→ SHORT EXAMPLE OF COMBINATORIAL PEPTIDE LIBRARY

1. Prepare solid supports bearing each of these amino acids

[Diagrams of H, V, S]
THIS IS OUR COMPILATION LIBRARY -

WE'VE QUICKLY PREPARED ALL POSSIBLE DIMERS CONTAINING H, V, S (9 COMPOUNDS)

FASTER THAN TRADITIONAL SYNTH!
NINE NEW COMPOUNDS MAY NOT SEEM SO IMPRESSIVE, BUT...

IF WE CONTINUE ADDING AMINO ACIDS, THE TOTAL NUMBER OF COMPOUNDS PREPARED RISES RAPIDLY.

NUMBER OF CMPDS IN LIBRARY

\[ N = b^x \]

\[ b = \text{number of different building blocks} \]

\[ x = \text{number of "cycles"} \]

\[ N = 3^2 = 9 \]

IF we repeat 5 more times

\[ N = 3^7 = 2187 \text{ cmpds} \]
THEN WHAT?

1. Bioassay these mixtures (either "on bead" or "off bead")
2. Find "winning" pool
3. Let's say "H-Z" vial shows activity

THEN WE KNOW

one of these molecules is a "winner"

To find winner: RESYNTHESIZE LIBRARY with H in final position

Bioassay — find winner

(Let's say HH is winner)
BETTER WAY TO FIND WINNERS!

- Remember (note) each bead contains a single compound!!
- We can bioassay a single bead "one bead - one stock method"

But...
- If we find a winning bead, how do we know what molecule was on that bead?
  (not enough on bead for NMR!)
How to identify the compound on a bead

As we synthesize the compounds on the beads we also add molecular "tags" to the polystyrene ... these tags provide a record of the reagents that the bead has "seen".

Tag 1 is a molecule that will uniquely tell us that the bead saw H coupled in "round one".
We must be capable of detecting these tags at very low concentrations.

Tags must be conveniently added to polystyrene bead as part of synthesis "cycle"

We'll need a large number of structurally distinct tags... one for each different reaction (pages 4 & 5 = six exps)

What are these tags?
What are these tags?

\[
\begin{align*}
\text{N} &= \text{N} = \text{CH} \quad \text{OCH}_3
\end{align*}
\]

\[\text{Rh}_2(\text{O}_2\text{CCF}_3)_4\]

Tag

Tag can be removed from bead by "cleaving" using ceric ammonium nitrate.

Varying \(n\) and \(x\) allows for a large number of structurally similar but chemically distinct tags.
Put a tag on the bead that uniquely identifies the reagents that the bead has "seen."

Let's track the life of winning bead in our assay.
many tags
Tag can be cleaved from bead and detected with high sensitivity by varying \( n \) and \( x \)

1. Round 1 H tag_1 \( n=3 \) \( x=3 \)
2. Round 1 V tag_2 \( n=41 \) \( x=3 \)
3. Round 1 S tag_3 \( n=5 \) \( x=3 \)
4. Round 2 H tag_4 \( n=3 \) \( x=4 \)
5. Round 2 V tag_5 \( n=4 \) \( x=4 \)
6. Round 2 S tag_6 \( n=5 \) \( x=4 \)

GC-MS used to "view" tags

1. Cleave Tags
   2. GC-MS

STDs

1 2 3 4 5 6

time

Etc.
Summary

- Quickly synthesized large library of cmpd
- Bioassay - one bead/one stock to find a winning bead (bearing a winning cmpd)
- Identify the chemical structure of the winning cmpd by clearing "tags" from bead, and looking at their identity using gas chromatography-mass spectrometry, and reading out the code.