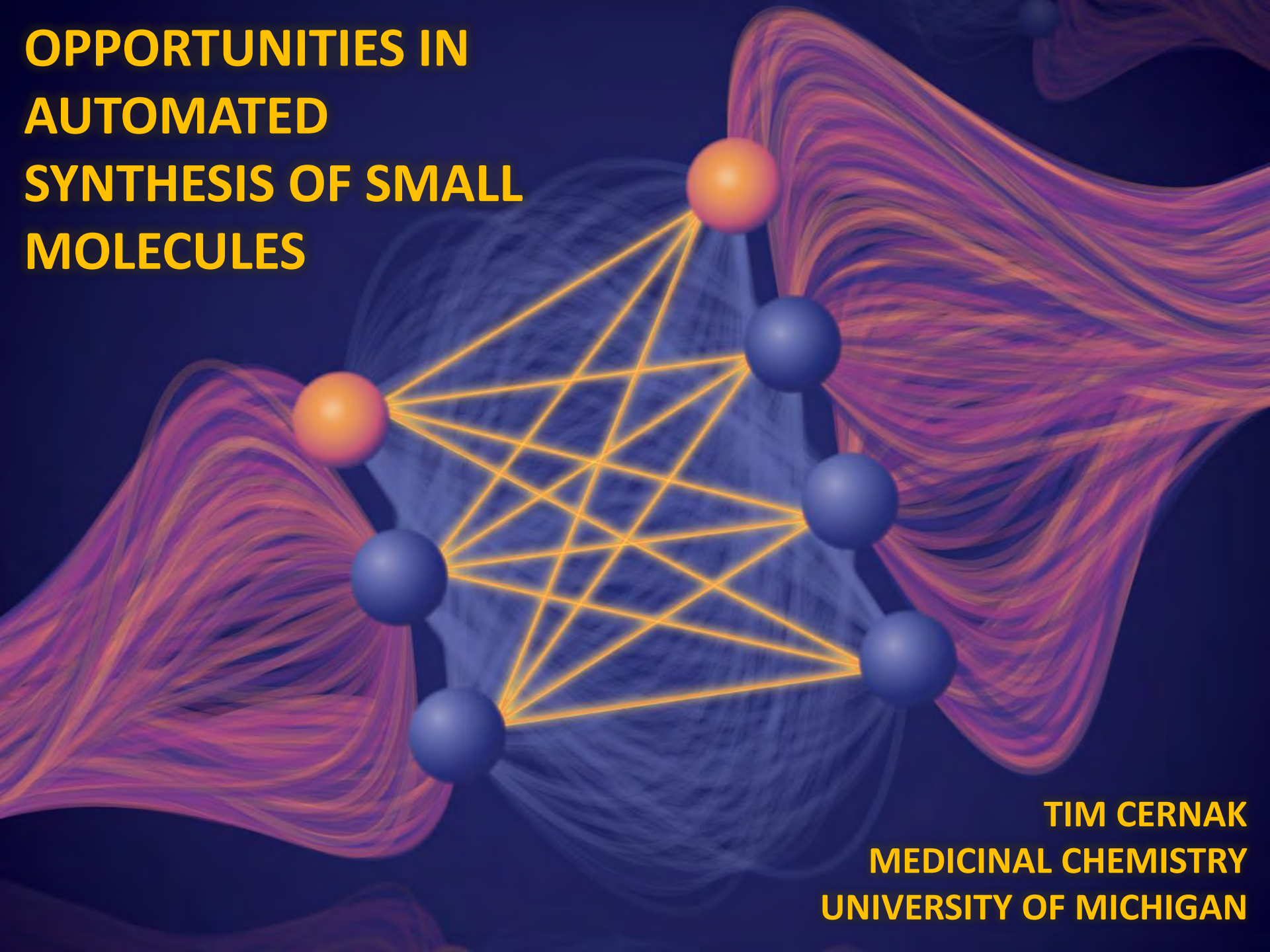
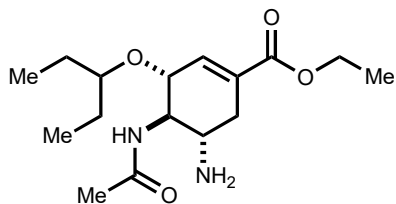


OPPORTUNITIES IN AUTOMATED SYNTHESIS OF SMALL MOLECULES



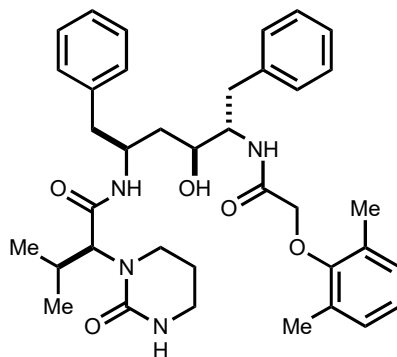
TIM CERNAK
MEDICINAL CHEMISTRY
UNIVERSITY OF MICHIGAN

MOLECULES IN CHEMICAL SPACE



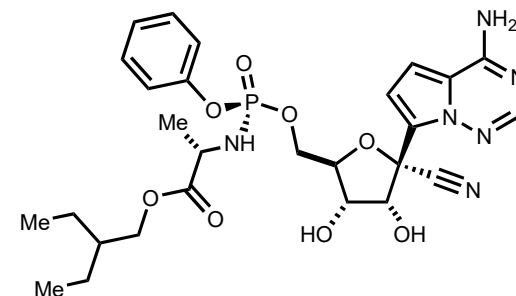
oseltamivir

```
O=C(C1=C[C@H]([C@@H]([C@H]
(C1)N)NC(C)=O)OC(CC)CC)OCC
```



lopinavir

```
O=C(N[C@H]([C@H](C[C@@H]
(NC([C@@H]
(N1C(N([H])CCC1)=O)C(C)C)=O)
CC2=CC=CC=C2O)CC3=CC=CC
=C3)COC4=C(C)C=CC=C4C
```

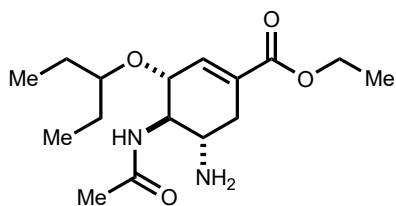


remdesivir

```
O[C@H]1[C@@H](O)[C@@]
(C2=CC=C3N2N=CN=C3N)
(C#N)O[C@@H]1CO[P@]
(OC4=CC=CC=C4)(N[C@@H]
(C)C(OCC(CC)CC)=O)=O
```

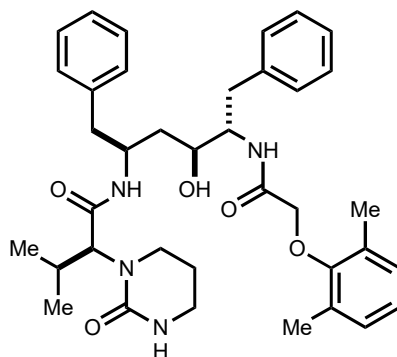
These antivirals are complex small molecules

MOLECULES IN CHEMICAL SPACE



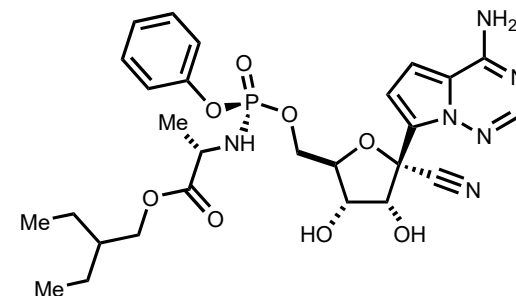
oseltamivir

```
O=C(C1=C[C@H]([C@@H]([C@H]
(C1)N)NC(C)=O)OC(CC)CC)OCC
```



lopinavir

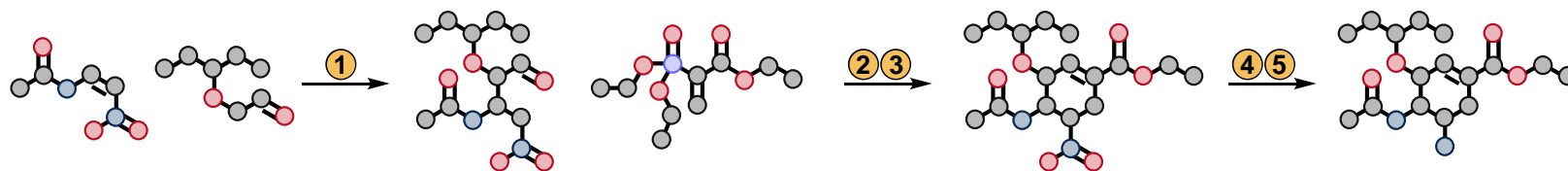
```
O=C(N[C@H]([C@H](C[C@@H]
(NC([C@@H]
(N1C(N([H])CCC1)=O)C(C)C)=O)
CC2=CC=CC=C2O)CC3=CC=CC
=C3)COC4=C(C)C=CC=C4C
```



remdesivir

```
O[C@H]1[C@@H](O)[C@@]
(C2=CC=C3N2N=CN=C3N)
(C#N)O[C@@H]1COP(=O)
(OC4=CC=CC=C4)(N[C@@H]
(C)C(OCC(CC)CC)=O)=O
```

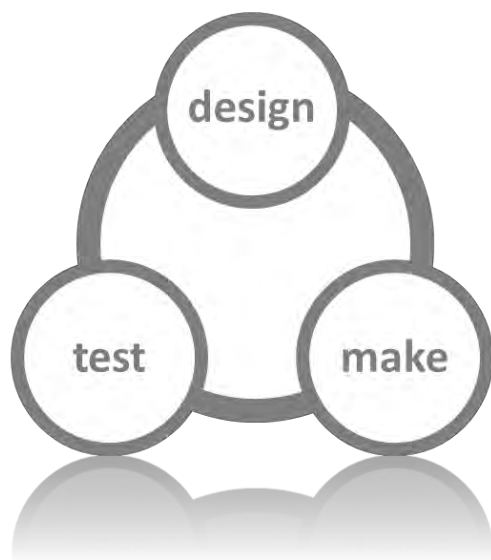
These antivirals are complex small molecules



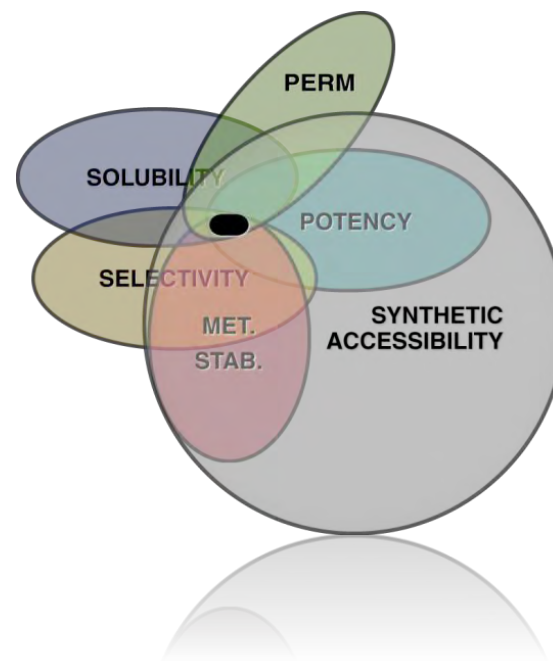
They are challenging to make with chemical synthesis
& require multistep total synthesis

CHEMICAL SPACE EXPLORATION

design cycle



objective



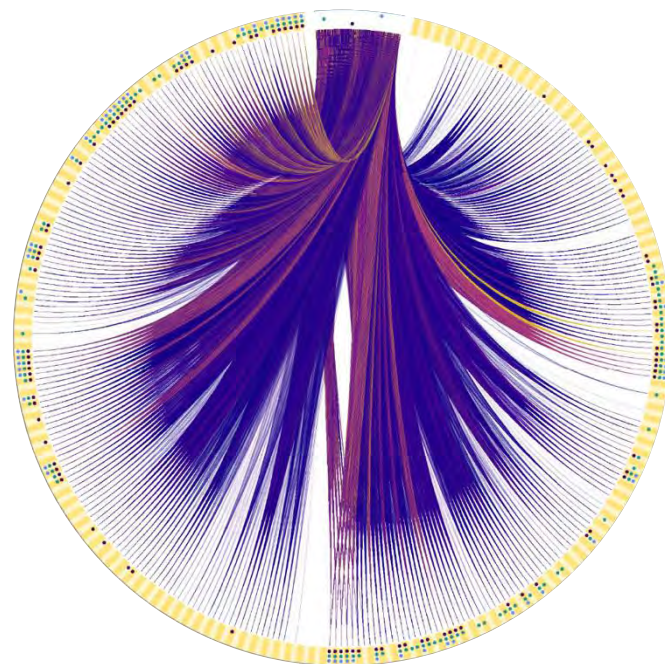
**chemical synthesis is an empirical science,
it is the bottleneck in the optimization of medicine**

AUTOMATING CHEMICAL SPACE EXPLORATION



nanoscale synthesis

Science, 2015, 347, 49
Nature, 2018, 557, 228
Science, 2018, 361, eaar6236
Science, 2019, 363, 405



reaction enumeration

Nature, 2020, 579, accepted

CHALLENGES & OPPORTUNITIES

- **Molecules can be described as graphs**
- **We cannot predict performance of reactions or bioassays, but automated synthesis with in-line bioassay is possible**
- **Synthesis is an art**
- **Data science is little known in chemical synthesis**
- **No available large-scale automation resource exists**



THE CERNAK LAB

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