

CSC
COMPUTATIONAL &
STRUCTURAL CHEMISTRY

A Sparse approach to Lead Optimisation

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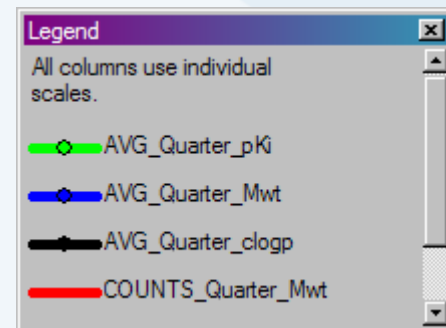
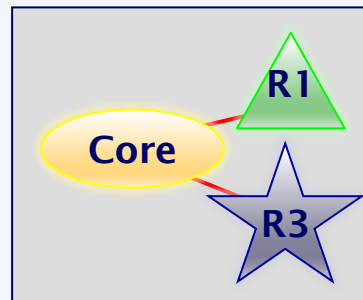
Lead Optimisation for a Target Programme

- **Asthma Target:**
 - No crystal structures available
 - SAR driven programme
- **Once-daily Oral Therapy:**
 - Activity in available assays
 - Primary SAR assays
 - Secondary Whole Blood assays
 - Appropriate disease model
 - Developability Profile:
 - Solubility
 - Molecular Properties: lipophilicity, MW
 - PK
- **Lead Identification:**
 - Diversity screening (HTS)
 - Focussed screening (Libraries etc.)
 - Knowledge-based design
- **Lead Identified!**

Optimisation of Lead Series

● Programme Achievements:

- 18 months intensive resource
- ~900 compounds made
- Whole blood potency
- Variable PK

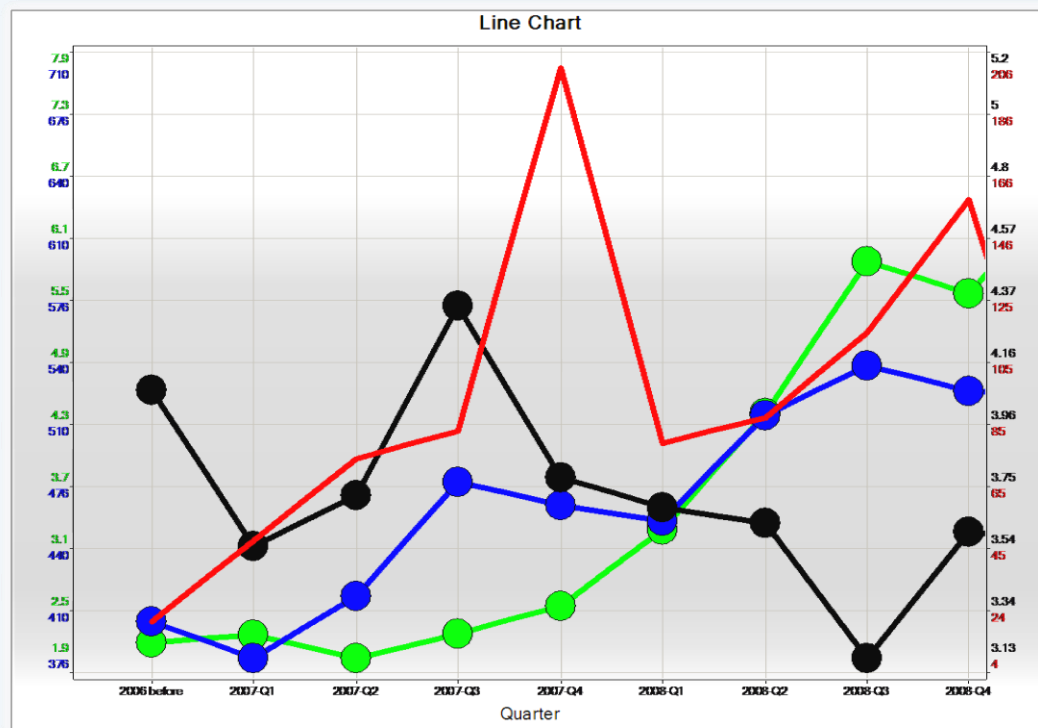


● Lead Molecule '521

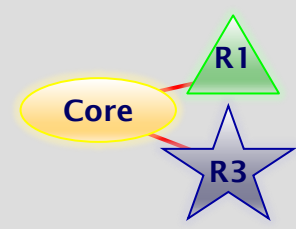
- Dec-06
- SPA: 6.1 LE: 0.35 LLE: 2.7
- WB: < 5.0

● Optimised Molecule '991

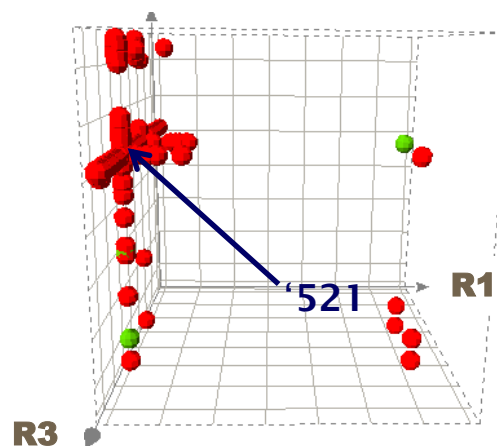
- May-08
- SPA: 7.5 LE: 0.31 LLE: 4.1
- WB: 6.2



SAR Exploration over time

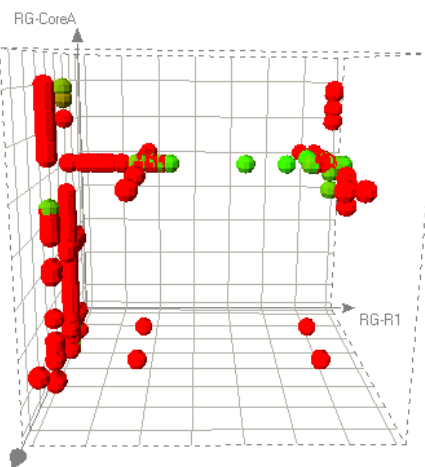


Core



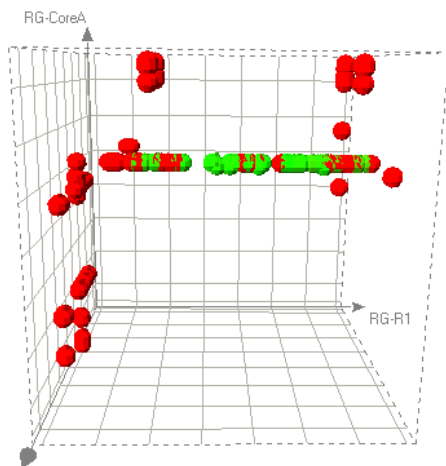
Pre June-07

- R3 exploration
- Core exploration
- Few actives



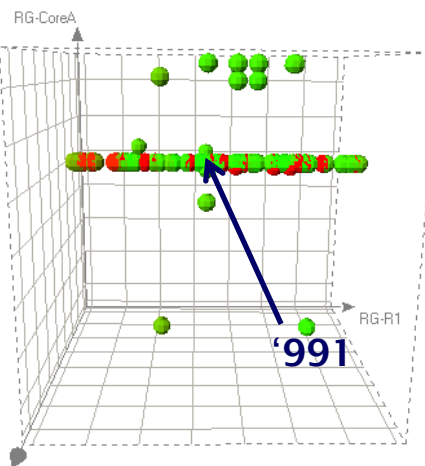
Post June-07

- R1 exploration
- More Core modifications
- Few R3 changes



Pre June-08

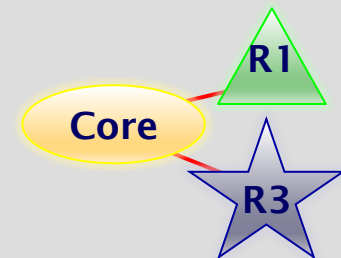
- Further R1 modifications
- Increased potency
- Limited core changes



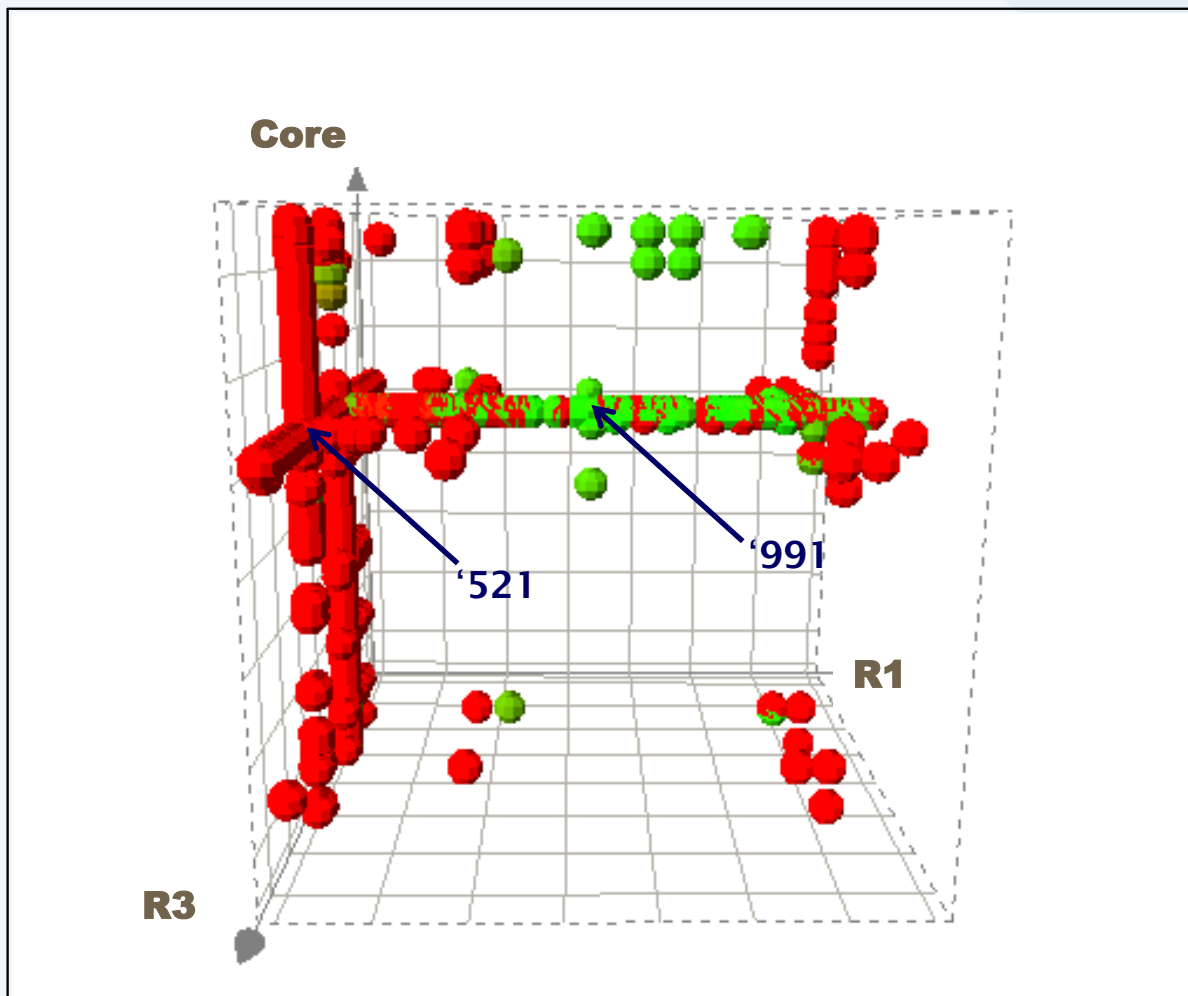
Post June-08

- More in-depth R1 investigation
- Some additional core modifications
- Mostly potent compounds

R-Group Decomposition of Series



- **R1 position (x-axis)**
 - 275 substituents
 - Lots of potency
- **R3 position (z-axis)**
 - 93 substituents
 - Few actives
- **Core (y-axis)**
 - 192 variants
 - Core and additional substituent modifications
 - Variable success



Considerations approaching Project Transition

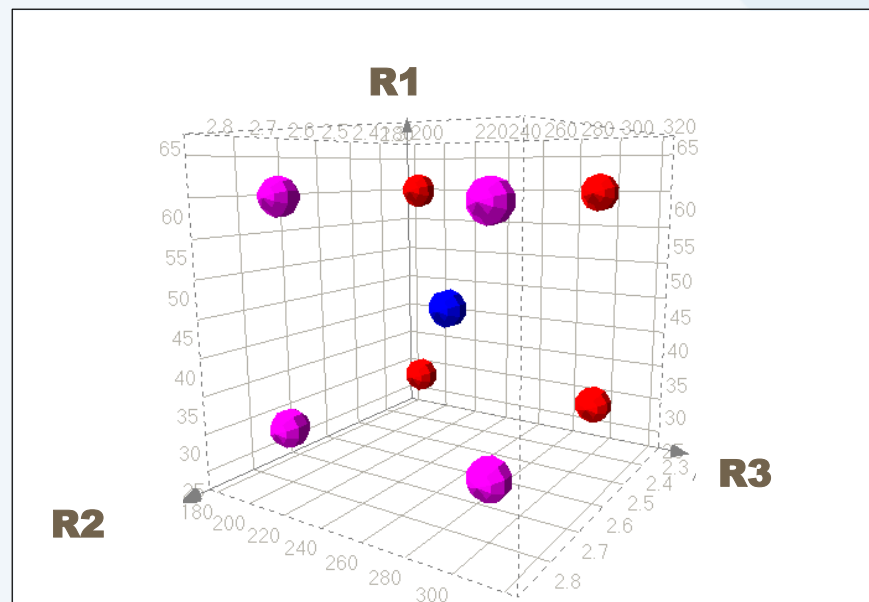
- Whole Blood potency
- Developability properties managed
- PK demonstrated

- SAR fully Understood?
- What else is left in this series?

- **Conclusion: Close out the series with SAR explosion array**
 - Build confidence in monomer contributions (SAR)
 - Look for alternate substituents
 - Optimise physicochemical properties
 - Look for additivity/cooperativity of the substituents.
 - Magic combination?

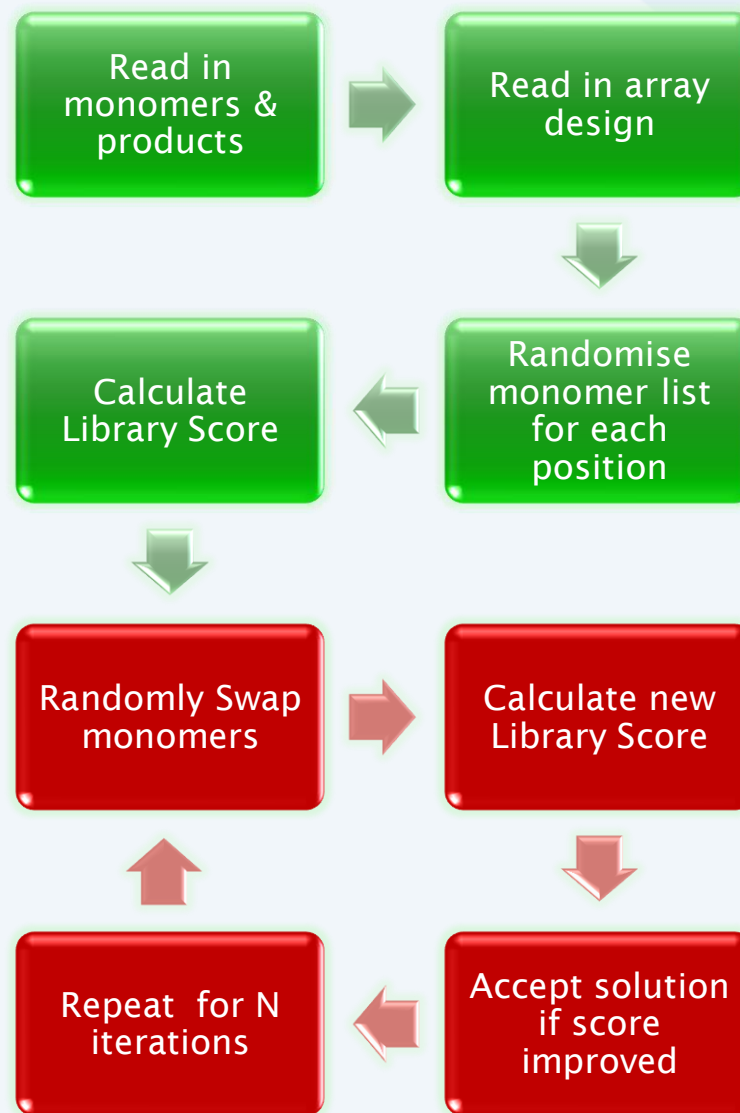
Experimental Design of Chemical Arrays

- **Experimental Design:**
 - Established technique for parametric experiments
 - Well-precedented for exploring continuous variables (time, pressure, temp)
- **Experimental Design for Arrays:**
 - Difficult to select monomers to fit continuous variable space
- **Balanced Fractional Designs:**
 - Monomers treated as categorical factors of design
 - Optimise monomer combinations to fit desired profile

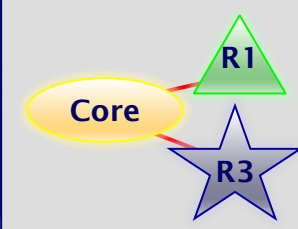


Array Design & Optimisation

- **Chemical Array Design:**
 - Determine chemical array space
 - Determine number of monomers for each dimension
- **Design Sparse Array:**
 - Decide on coverage/redundancy for each dimension
 - Generate balanced design
- **Populate the Sparse Array**
 - Determine optimisation parameters
 - Score-based local search optimiser[#]

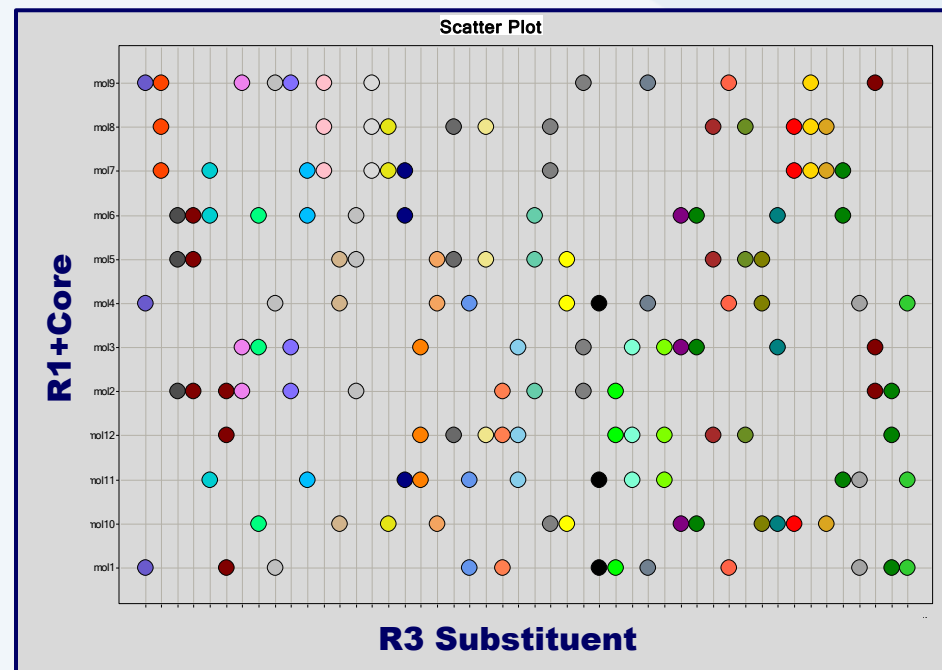


Sparse "Patchwork" Array Design



- **R1 + Core:**
 - Essential for potency
 - Synthetically challenging
 - Main area of Med. Chem. Exploration
 - *Focus on precedented cores*

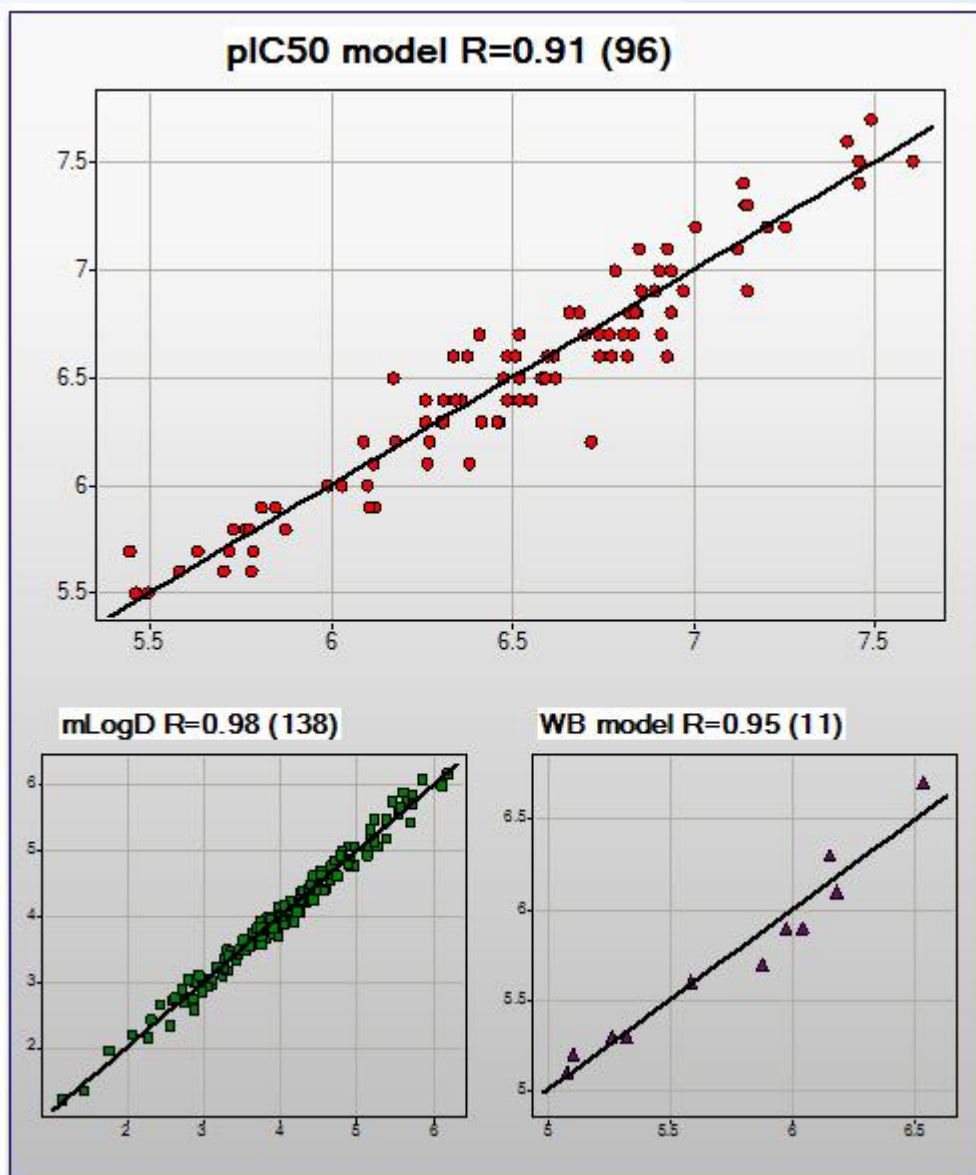
- **R3 Substituent**
 - Not explored recently
 - Chemically tractable
 - Significant drain on the molecular budget:
 - Halogenated aromatic
 - Acidic pKa
 - Lipophilic region
 - *Diverse/property-driven selection*



- **144 Sparse Compound array (1/4 fraction of 576)**
 - 12 synthetically intensive cores of interest
 - 48 R3 substituents
 - 576 array coverage
 - Diversity optimised design

Results:

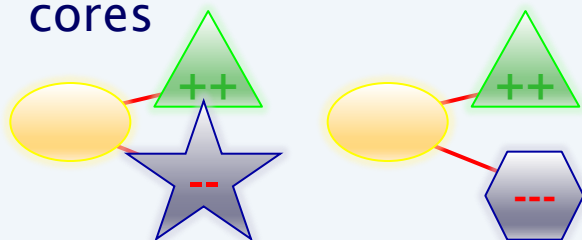
- **142 of the 144 compounds successfully synthesised**
 - 12 Core/R1 synthesis in several phases (rate limiting!)
 - Called on all available chemistry Resource
 - Significant quantities required
 - 12 R3 couplings completed reliably
- **Compound Progression:**
 - All compounds progressed to primary assay
 - Standard PhysChem measurements
 - LogD, Solubility
 - Secondary assays only for interesting compounds
- **FW Models:**
 - SAR highly additive
 - Little interaction between monomers
- **Classical QSAR models**



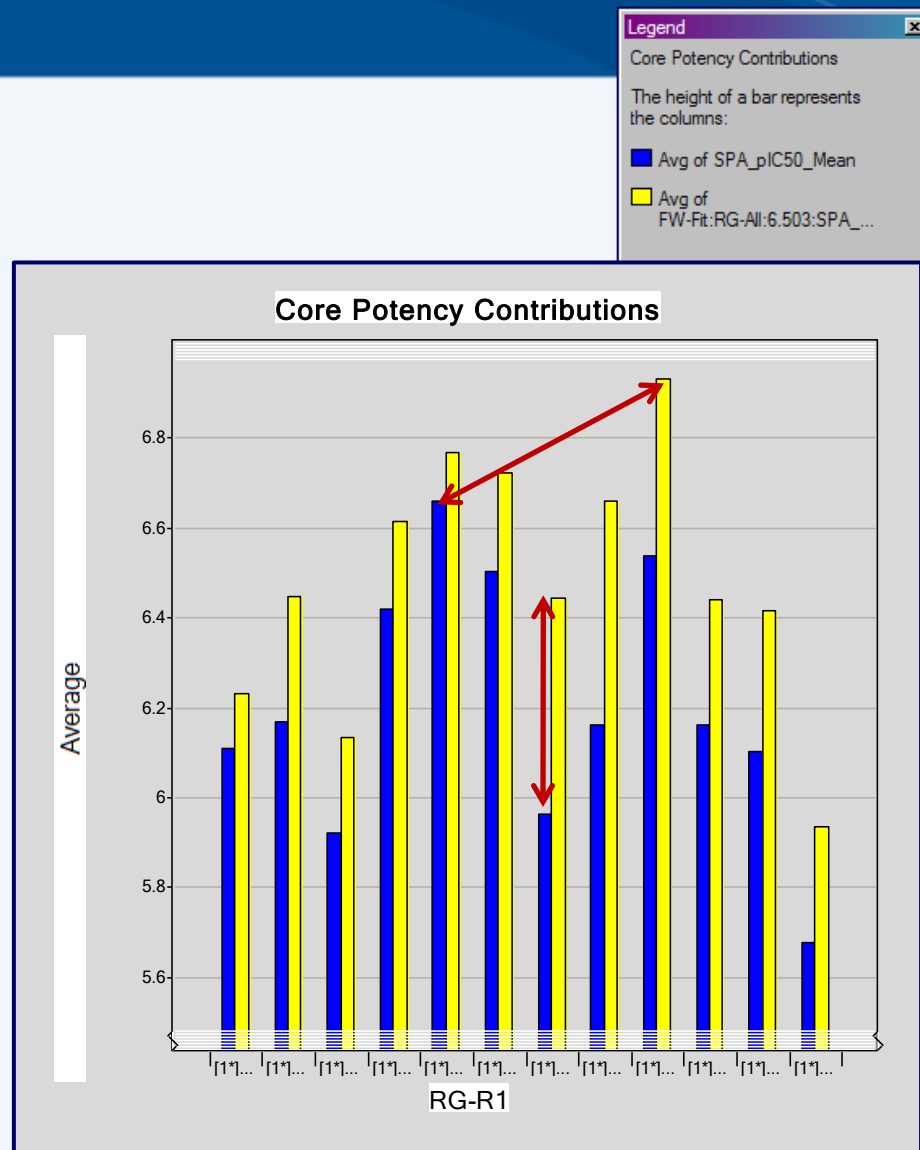
Monomer Rescue

● Average potency \neq Potency Contribution

- Good monomers hidden by poor context
- Less active substituents compensated with active cores



- Up to 0.5 units increase through use of model
- Situation would be worse with fewer active molecules

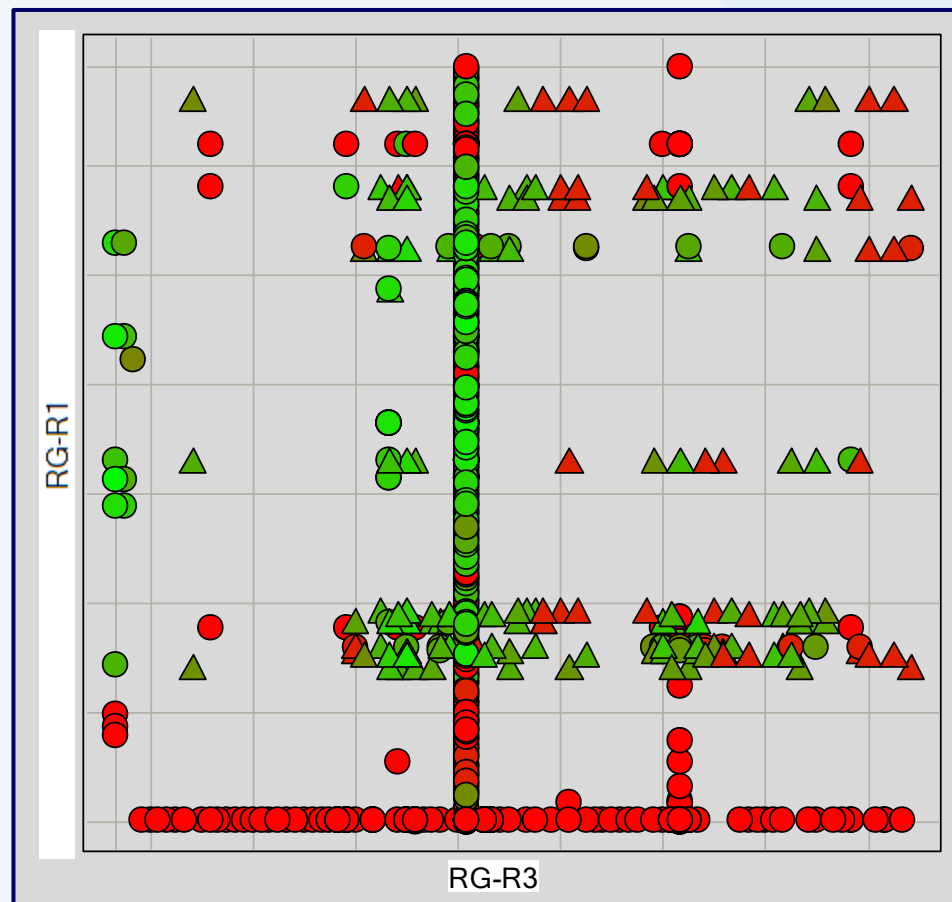


Compounds based on Predictions:

ID	Pred_SPA	SPA_Mean	Pred_LogD	mLogD	Pred_WB	WB_Mean
Cpd 1	7.6	7.6	5.1	5.3	5.6	
Cpd 2	7.6	7.6	3.7	3.8	6.2	6.4
Cpd 3	7.5	7.5	5.6	5.7	5.5	
Cpd 4	7.4	7.3	5.3	5.7	4.7	
Cpd 5	7.4	7.0	4.6	4.4	5.9	
Cpd 6	7.4	7.1	3.9	3.6		5.4
Cpd 7	7.4	7.0	3.9	3.6		
Cpd 8	7.3	7.3	3.5	3.6		
Cpd 9	7.3	7.4	4.4	4.4	6.0	
Cpd 10	7.3	7.4	3.6	3.5	6.4	
Cpd 11	7.0	6.6	4.5	4.8		
Cpd 12	6.9	7.0	4.4	4.0		
Cpd 13	6.9		4.1	3.8		
Cpd 14	6.8	6.8	4.2	4.3		
Cpd 15	6.8	6.7	3.8	3.6		
Cpd 16	6.8	6.4	5.0	5.3		
Cpd 17	6.6	6.5	4.2	3.8		
Cpd 18	6.4		4.8	4.3		

Outcomes...

- ... for the chemistry:
 - Alternate substituents identified
 - More efficient substituents uncovered
 - No break-through compounds identified
 - Synthesis scaled-back after this exercise
- ... for the programme:
 - Models highly predictive of WB assay
 - Intermediate assay terminated
 - Project transitioned with greater confidence



Sparse Arrays for Lead Optimisation

- **Practical considerations:**

- Complete design up-front required
- Challenging synthetic effort
- Sufficient (?) compounds must be made -> tested
- Chemistry and Chemists must be amenable to parallel chemistry

- **Pragmatic considerations:**

- Multi-dimensional arrays rarely exploited in Lead. Op.
- SAR explosion of greater value early in LO but need active compounds
- Potentially easier to synthesise a complete array?
- Difficult to support assays of less interesting compounds

- **Successful approach for exhausting a chemical series:**

- Efficient exploration of chemical space
- Perfect dataset for building robust models

Sparse Arrays in Medicinal Chemistry

- **Less compounds synthesised:**
 - Also less purification, screening, storage
 - Lower intermediate & monomer consumption
- **High Quality Datasets:**
 - Information rich
 - Good for model building
 - Increased SAR understanding
- **Effective exploration of chemical space:**
 - Comprehensive exploration of early series
 - Exhaustive exploration of established series
 - Efficient libraries
 - Condensed screening collections