Drug Repositioning

Cresset European User Group Meeting

21st June 2012

Repositioning-some definitions

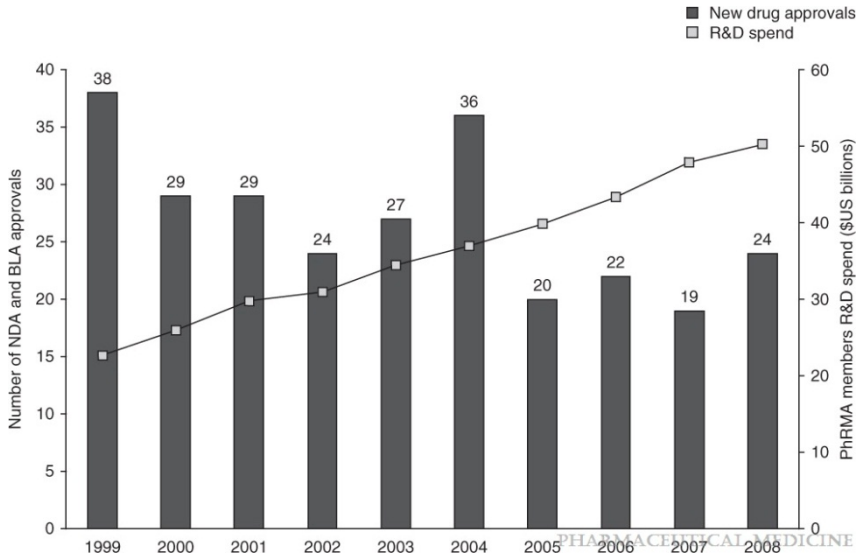
"*The most fruitful basis for the discovery of a new drug is to start with an old drug*"
Sir James Black, Winner of the 1988 Nobel prize in Physiology and Medicine

- New opportunities (lower risk) based on existing drugs and their templates
- Many names-same thing: Repurposing, Reprofiling, Therapeutic switching, New Uses for Old Drugs (NUFOD).

New understanding in biology/medicine/chemistry driving innovation

Advantages-Why do it

- Classical drug discovery and development is getting harder



- Rising development cost
- High rates of attrition due to Toxicity and Lack of efficacy
- Increasingly stringent regulatory demands
- Difficulty in recouping R&D spend
- Many key products reaching patent cliff's

Advantages

- Advantages are based on greater knowledge of agent compared to classical NCE discovery (toxicology, clinical safety, pharmacokinetics)
  - Less likely to fail from Tox, Clinical Safety, ADME
  - Potential for rapid approach to POC
  - Early kill points-fail early-fail cheap
  - Maintain markets through new patents
  - Can be faster to approval
- Commercially Valuable?
  - Highest selling Pharmaceuticals in USA
    - Nexium (single enantiomer Omeprazole) -2nd highest
    - Adavir(Inhalation combo Salmeterol & Fluticasone)-4th Highest
  - Sildenafil: hypertension≈ ED, Raloxifene: Breast Cancer ≈Osteoporosis, Milnacipran: antidepressant ≈fibromyalgia & etc..
  - Reprofiling development can profit from reduced development costs making it easier to recoup R&D costs

Advantages-many companies Different Discovery Platforms

Company	Founded	Repurposing platform	Source of repurposing candidates	Examples of clients
BioVista Inc. (www.biovista.com)	1993	Literature analytics: proprietary database capturing reported research findings, US FDA adverse event reports and proprietary experimental data for exploring biological correlations	Pharma clients	Biogen idec, Novo Nordisk, Roche, Wyeth, Exelixis
KineMed (www.kinemed.com)	1999	KineMarkers: *in vivo*, stable isotope kinetic biomarkers that measure the flux of molecules through complex and therapeutically relevant biological pathways	Pharma clients	Roche, Merck KGaA, Bayer, Organon, CMIC Co. Ltd, Sosei
Ore Pharmaceuticals (formerly Gene Logic) (www.orepharma.com)	1993	Platform no longer in use (previously included genetic expression profiling; metabolomics; *in vivo* imaging; *in vitro* cell-based assays; databases and data mining)	Pharma clients	Lundbeck, Roche, Millennium Pharmaceuticals
Melior Discovery/ Pharmaceuticals (www.meliordiscovery.com)	2005	Multiplexed *in vivo* assays validated in the pharma industry	Pharma clients	Pfizer, Merck & Co., Johnson & Johnson, AstraZeneca, Cephalon
Numedicus Ltd (www.numedicus.co.uk)	2008	Compound Analysis for New Drug Indications (CANDI) database to identify new uses for existing drugs	Pharma clients	Not disclosed
Sosei (www.sosei.com)	1990	Drug reprofiling platform: access to a wide variety of assays/models through collaborations	Library of drug candidates, drug templates and stalled development compounds, including drugs marketed in Japan but not in western markets	NeuroSolutions Ltd

Many Techniques

- In-Silico Approaches e.g.
  - Biovista Inc: Integrated predictive Dbase, literature text mining, and adverse event information to predict new indications and toxicities-collaboration with FDA
  - Numedicus:Compound Analysis for New Drug Indications-CANDI)
- Wet Lab & Combined approaches e.g.
  - Melior Discovery: Multiplexed (35) *in-vivo* assays across a range of Indications e.g inflammation, diabetes, dermatology (10 weeks)
  - CombinatoRx: Dbase-Chalice and high throughput cell based assays looking for synergies between agents to predict combination therapies.

Personal Experience

- Chiroscience-Celltech, Arakis-Sosei, Serentis etc.

Two Repositioning Strategies

- Non-structure based: Identification of repositioning opportunity based on literature mining relevant pharmacological observations, but not based on structural template
- Structure based: Identification of repositioning opportunity based on structural template

Examples from the past -Non Structure based

- NVA 237-Arakis/Sosei-Vectura –Licensed Novartis
  - Identification of clinical need for long acting, safe inhaled anti-muscarinic bronchodilator for COPD
  - Identification of existing (old) IV medicine as inhaled therapy for COPD-good safety profile and long action-Glycopyrronium Bromide
  - Rapid cost effective development to POC and FDA agreement for reduced non-clinical programme.
  - Significant licensing deal with Novartis-NVA237 Phase III completed, intended launch 2012 EU, 2014 USA
  - Good example of identification of clinically and commercially attractive programme

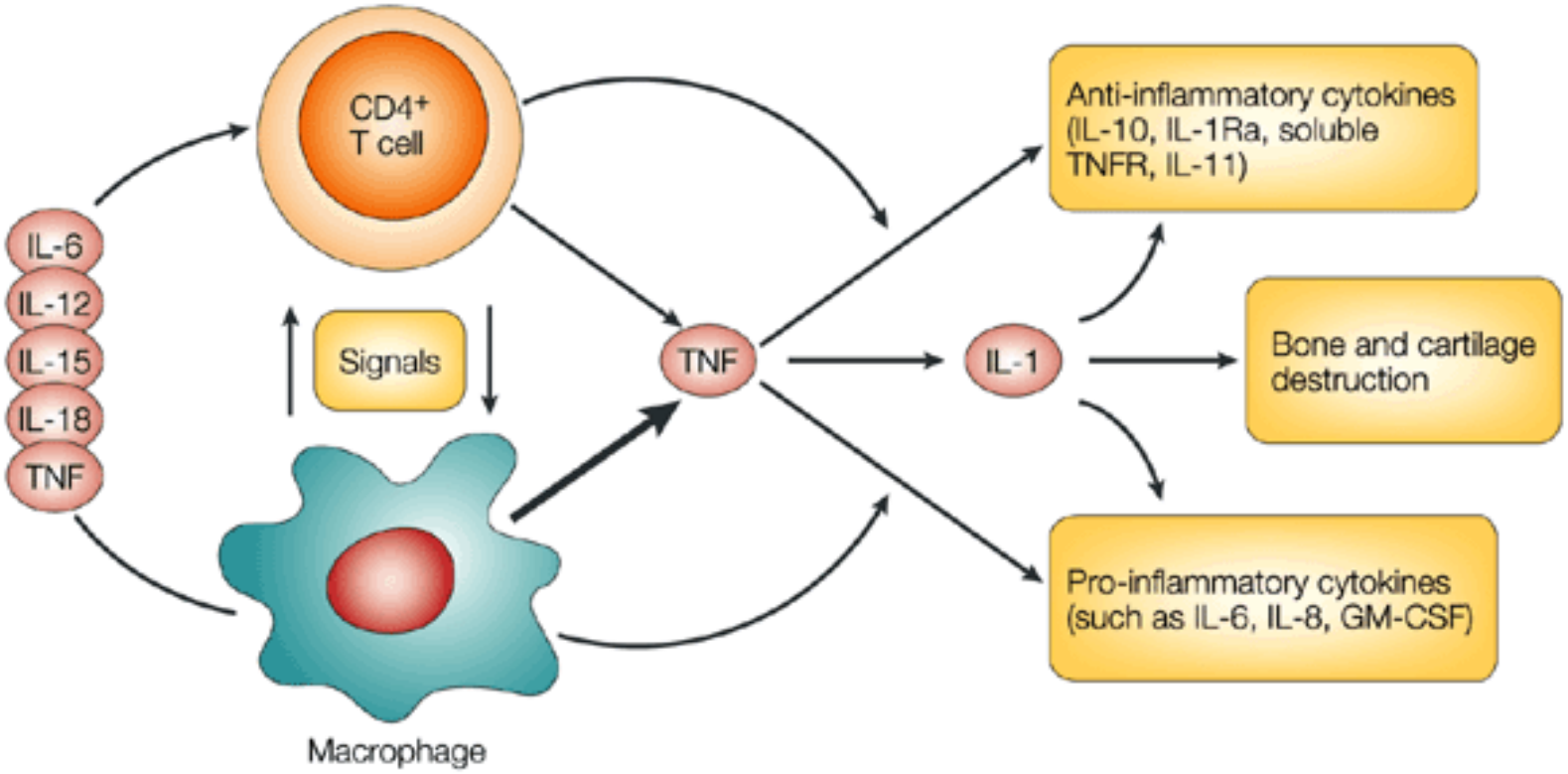
  But
  - Complex argument re-IP made licensing difficult
  - Single product play
- Chirocaine-Chiroscience
  - Reprofile of single enantiomer (L) of existing medicine bupivicaine for improved safety
  - Only marginal improvement in safety
  - Licenced to NAPP/Purdue

  But
  - Lower value licensing deal based on limited safety advantage
  - Single product play

Reprofiling- Non Structure based Cons

- Can be difficult to identify other pharmacologically relevant molecules from the Pharmacopeia- limited understanding of the Pharmacophore
- One shot-single drug play
- IP generation-literature based identification can "teach you too much"-the prior-art trap
- Chemical optimisation and generation of NCE follow on agents difficult without understanding of the pharmacophore

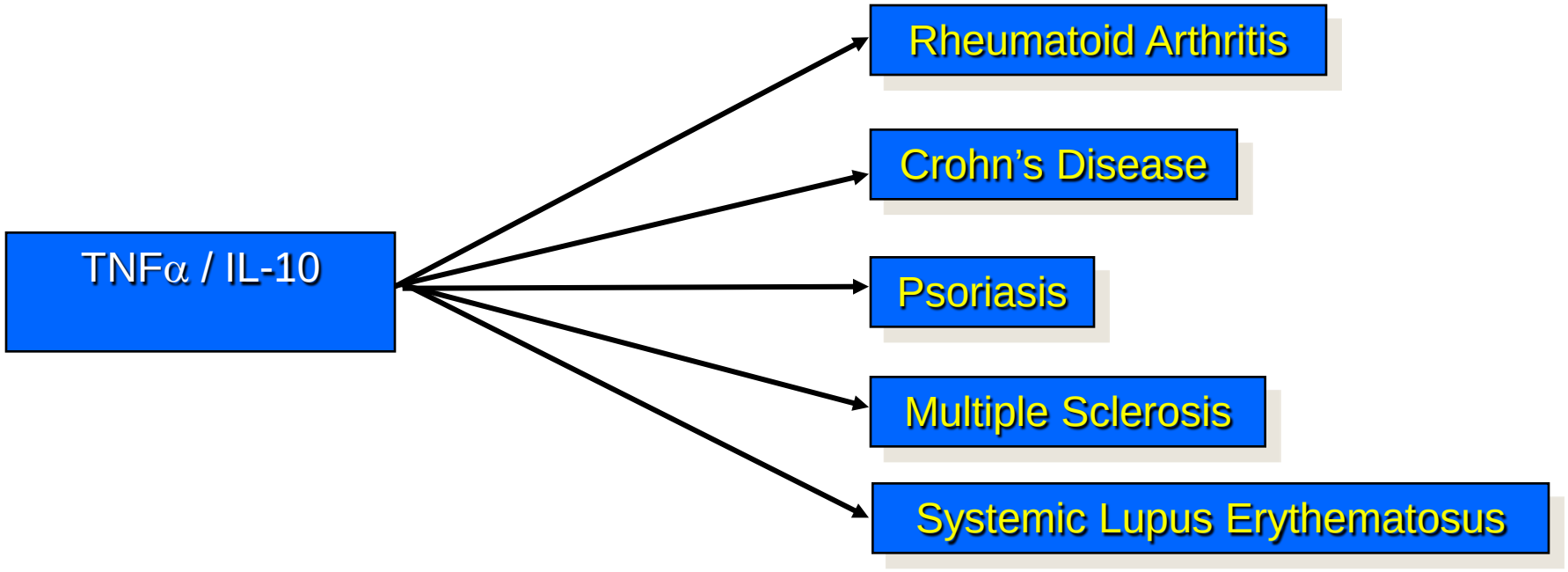
An example from the past structure based repositioning based-IL-10 and TNFα Modulation



Inhibiting pro-inflammatory TNF and promoting anti-inflammatory IL-10, Cytokine re-modulation is a valid strategy

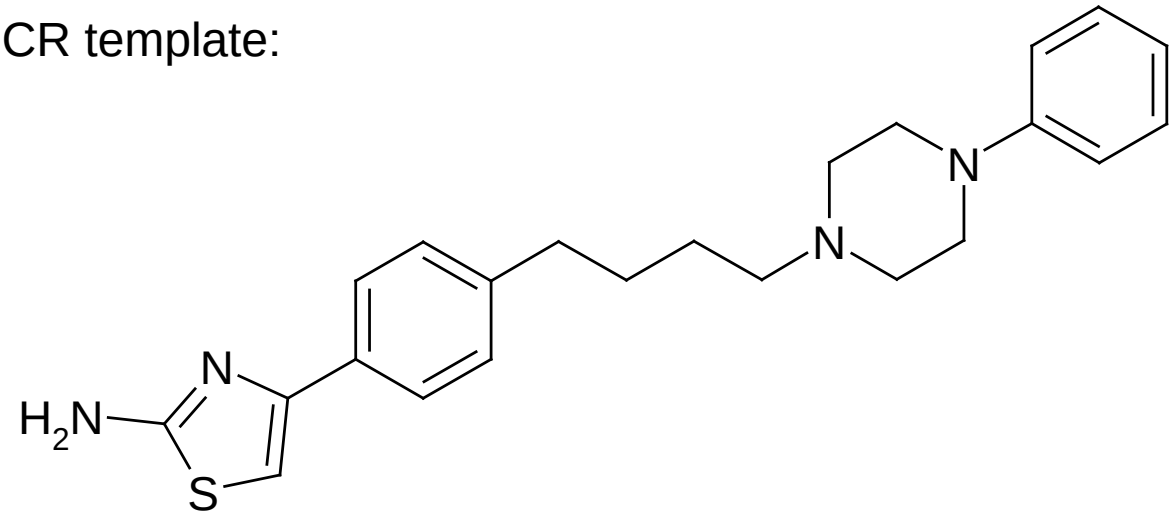
Nature Reviews | Immunology

Multiple Endpoint Opportunities For Cytokine Modulators



Modulation of TNFα / IL-10

Selection of GPCR template:

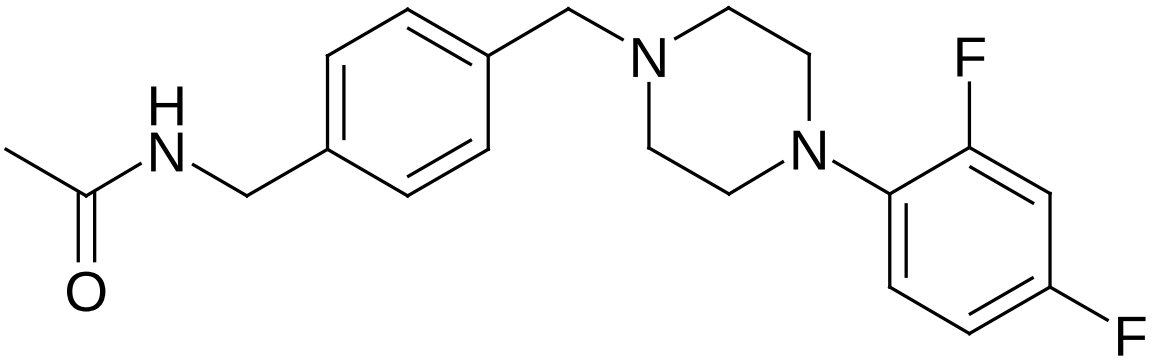


D2	5HT1A	5HT2	α1	TNFα	IL-10
5.5nM	3.8nM	37.0nM	7.9nM	87% Inhib.	382% control

T Hanano *et al*, *Bio-org. Med. Chem. Letts*., 2000, 10, 875

Modulation of TNFα / IL-10

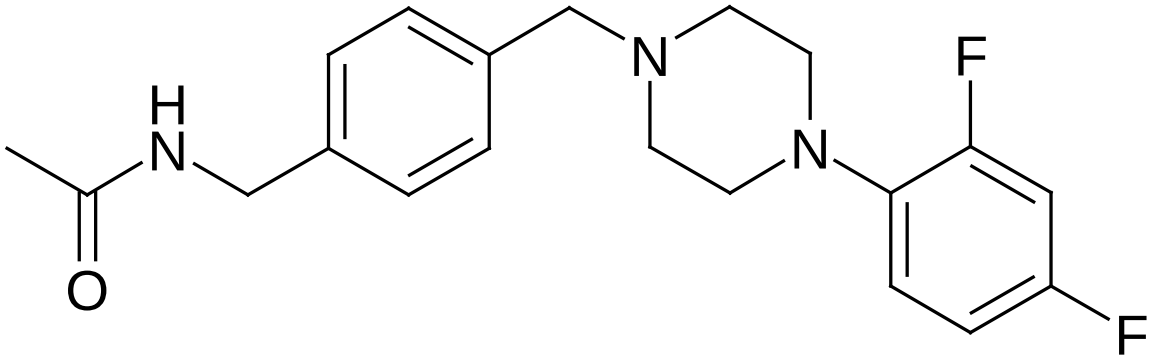
Refinement of GPCR template:



D2	5HT1A	5HT2	α1	TNFα	IL-10
> 1μM	> 1μM	> 1μM	> 1μM	91% Inhib.	2293% control

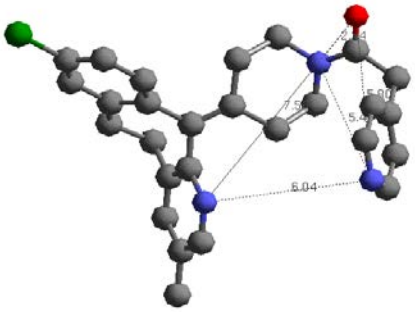
T Hanano *et al*, *Bio-org. Med. Chem. Letts*., 2000, 10, 875

Novel Cytokine Modulators from 'Drug-like' Templates



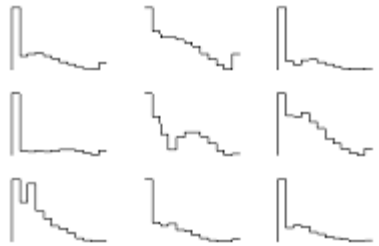
- 'GPCR like' ligand with no characterised GPCR activity.
- Potent inhibitory effect on TNFα (anti-inflammatory)
- Potent enhancement of IL-10 (Immunosupressant)
- *In vivo* efficacy demonstrated in LPS mouse and in adjuvant arthritis.
- Utilise virtual screening to identify novel anti-cytokine templates.

Virtual Screening for GPCR like Cytokine Modulators-BioPrint

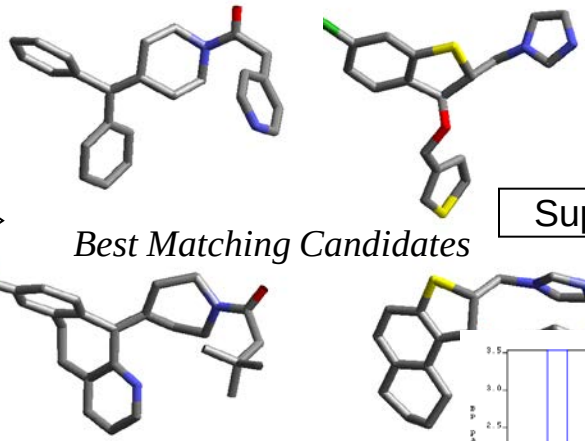


3D-Model of Compound ...

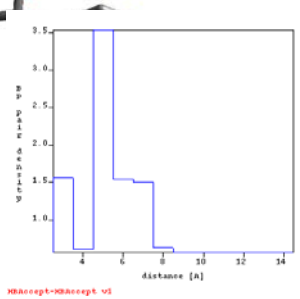
Comparison



Pharmacophore Fingerprint Database

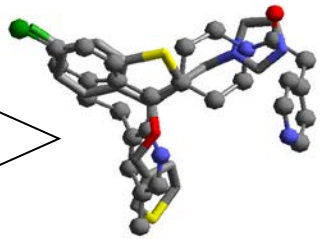


Best Matching Candidates



Superposition

Most Similar Candidates



Structure based-reprofiling
The advantages

- Easier Identification of relevant molecules from the pharmacopea-not limited by literature trawling for observations of relevant pharmacology

- Greater opportunity to develop a robust IP position

- Potential for multiple opportunities from single concept

- Greater potential for value augmentation by chemical optimisation. Known Drug to NCE

Summary

- Repositioning is a valid and valuable adjunct to classical drug discovery.
  - Lower risk
  - Rapid and cost effective-easier to recover development costs
- Both structure and non- structure based approaches are valid But:-
- Structure based approaches have many advantages
  - Identification of molecules in the absence of literature
  - IP
  - Multiple opportunities
  - Potential to act as the basis for the design of NCE's
- Development of sophisticated data mining tools and computational chemistry approaches will enhance the productivity of drug repositioning.