

## AstraZeneca Discovery Review



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Head of Global Discovery Research

### Delivery of CDs - improving productivity

- ↳ 'Humanising' discovery
  - ↳ Front-loading risk
  - ↳ High quality standards
  - ↳ Global working
- } More, better, faster



## 'Humanising' drug discovery

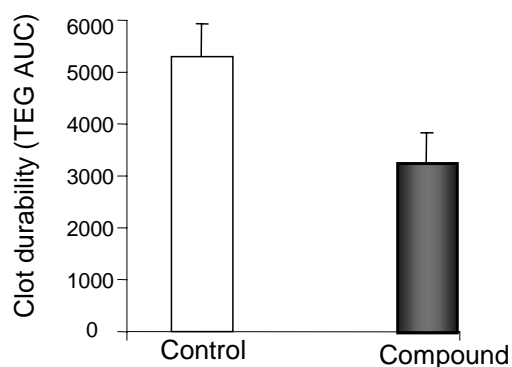
### Integrating patient and pre-clinical information

- ◆ new targets from human tissues
- ◆ translational models
- ◆ predictive response markers
- ◆ appropriate patient populations
  - early data in man
  - re-rationalise disease definition
  - clinical benefit > side effects

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## 'Humanising' drug discovery:

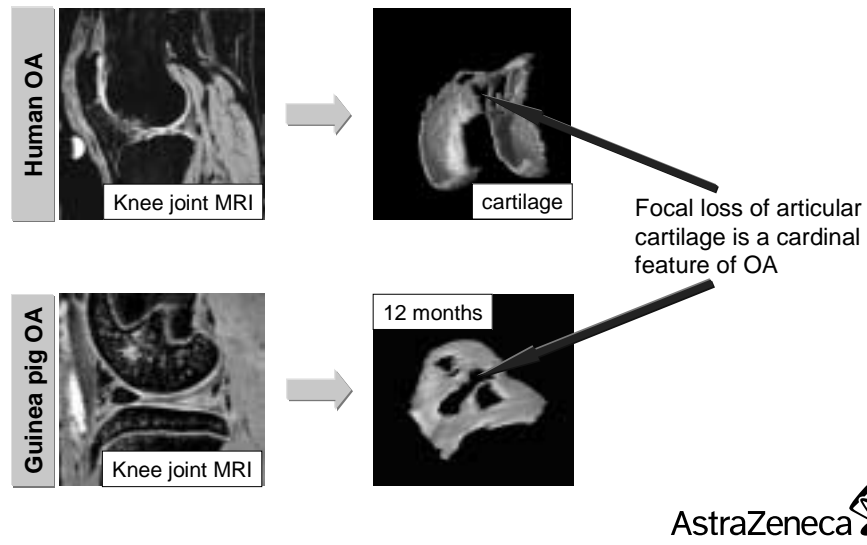
New target from human tissue



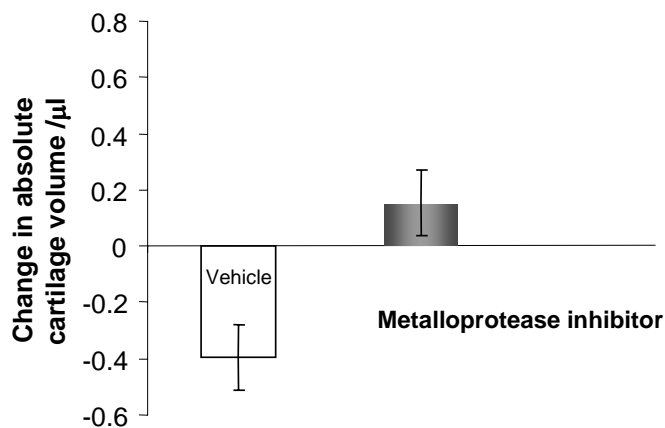
Dissolution of blood clots in obese individuals with impaired fibrinolysis

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## 'Humanising' drug discovery: Translational models in drug testing

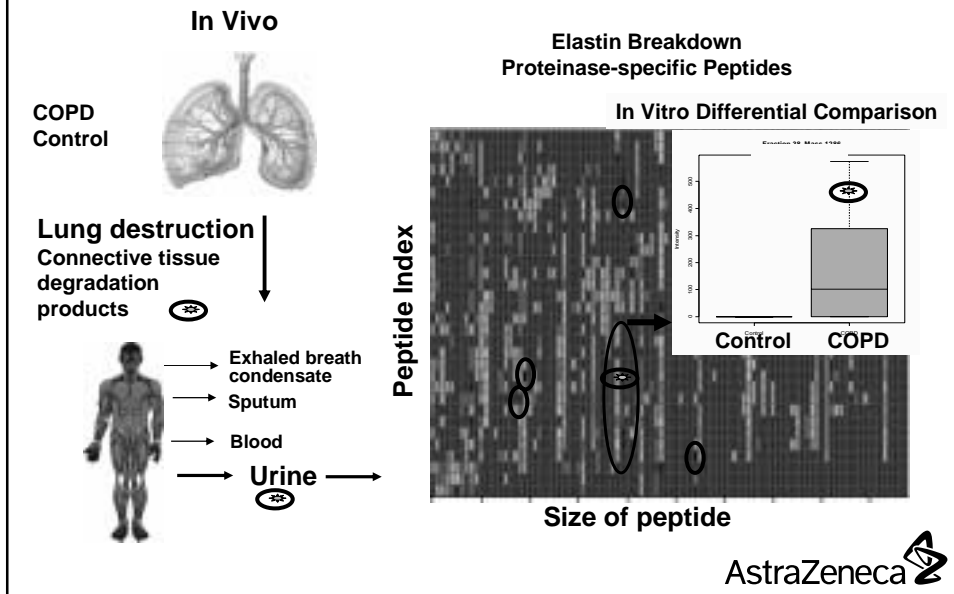


## Metalloprotease inhibitor prevents cartilage loss in Guinea Pig Model OA



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## 'Humanising' drug discovery: Predictive response marker in COPD

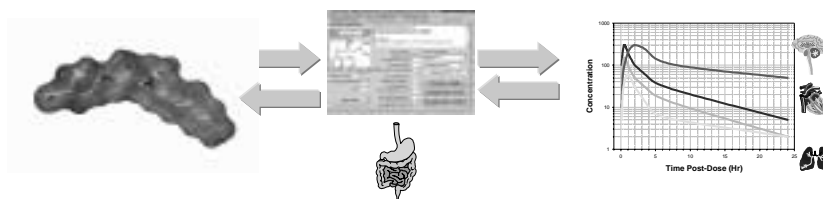


## Delivery of CDs - Improving productivity

- 'Humanising' discovery
- Front-loading risk

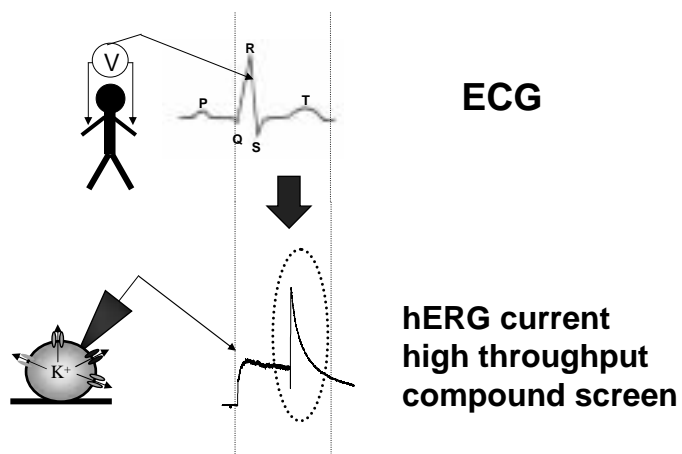
## Front-loading DMPK and toxicology

- Earlier DMPK and toxicity studies
- Development of bio-markers
- Predictive *in silico* modelling of DMPK and toxicity



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## Reducing risk for cardiac complications



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## Delivery of CDs - Improving productivity

- ↻ 'Humanising' discovery
- ↻ Front-loading risk
- ↻ High quality standards

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## Criteria for quality CDs

- ↻ Potent, selective, specific at validated targets
- ↻ Efficacy in validated animal models
- ↻ Bioavailable and predictable kinetics
- ↻ Extensive Safety package
- ↻ Biomarker development
- ↻ Low formulation & manufacturing risk
- ↻ Strong IP
- ↻ Differentiated vs. current therapy and competition

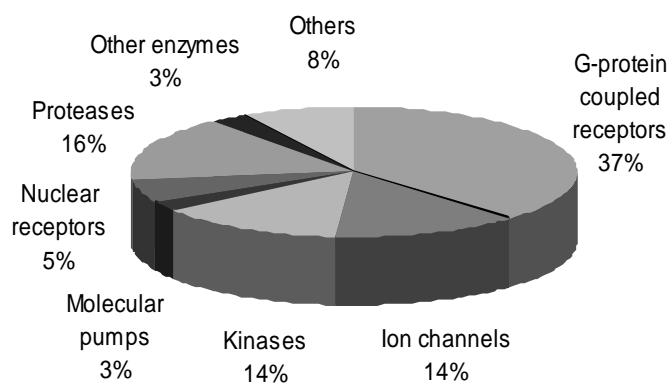
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## Delivery of CDs - Improving productivity

- 🔗 'Humanising' discovery
- 🔗 Front-loading risk
- 🔗 High quality standards
- 🔗 Global working

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## Target class initiatives



**Efficient lead generation and mechanistic understanding across disease areas**

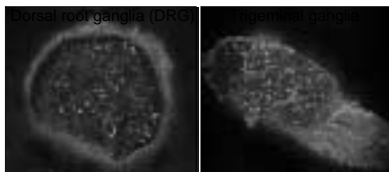
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## GPCR database: Integrating biology and chemistry

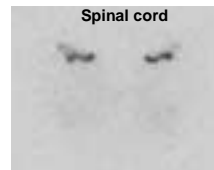
The screenshot shows the AstraZeneca GPCR Database website. At the top, there is a navigation bar with 'GPCR Database' and 'Phase 2' tabs. Below this, the main content area is divided into three columns: 'Receptor Information', 'In Situ Hybridization', and 'Screening'. Each column has a 'What's new?' section with bullet points and a 'Search' section with a 'Quick Search' box. The AstraZeneca logo is visible in the bottom right corner.

## Sensory neuron specific GPCRs

mRNA



Protein



Ligand identified

**Proenkephalin A gene products  
activate a new family of sensory  
neuron-specific GPCRs**

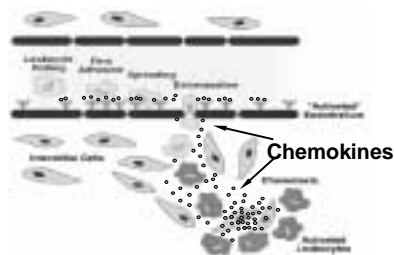
*Nature Neuroscience* **5**, 201-209 (2002)

**Pain relief without systemic side effects**

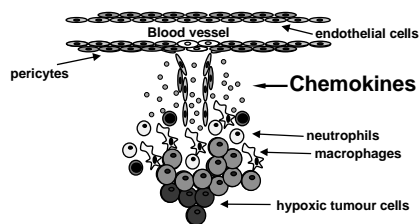
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## Chemokines: A GPCR subfamily

### Leukocyte recruitment and activation



### Angiogenesis

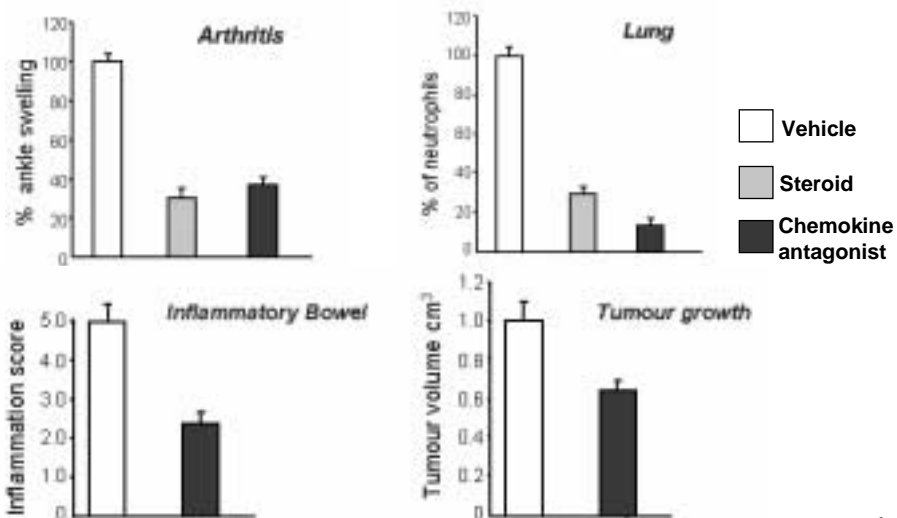


Nelson & Krensky Immunity 14, 377-386, 2001

6 CDs since 2000 – more to come

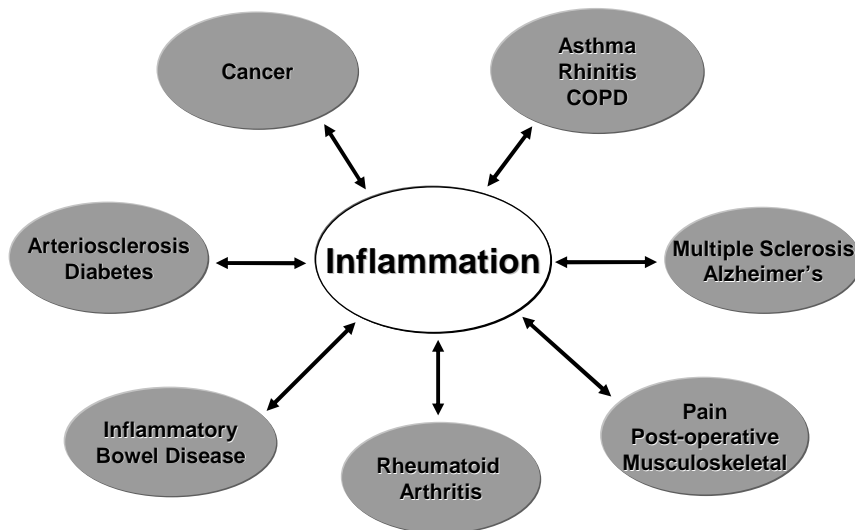
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## Multiple indications for a chemokine antagonist - effects in disease models



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## Inflammation asset exploitation

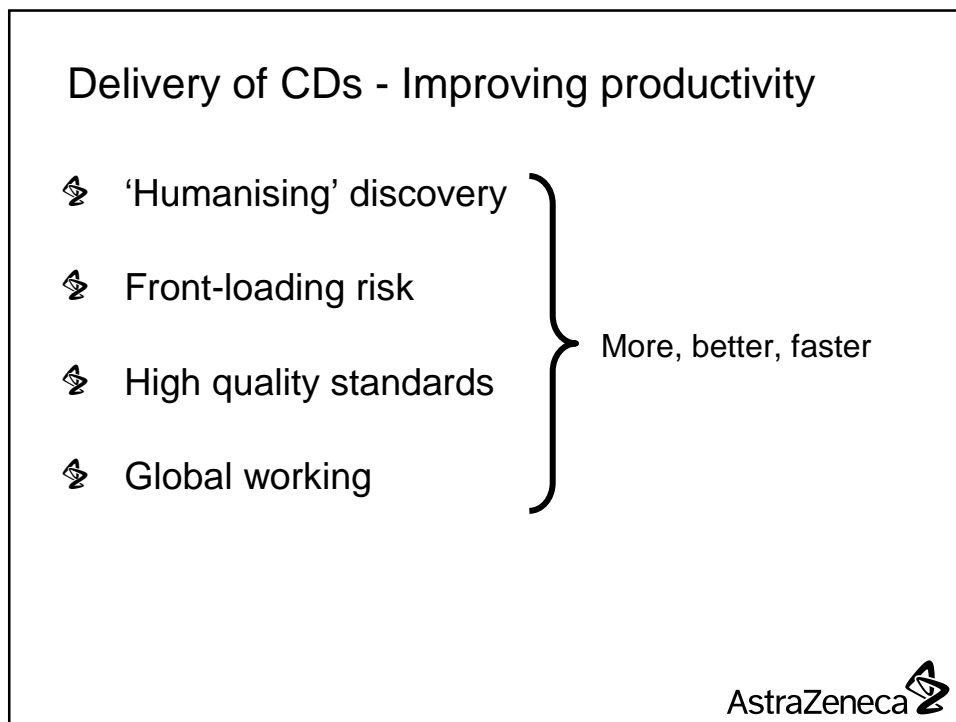
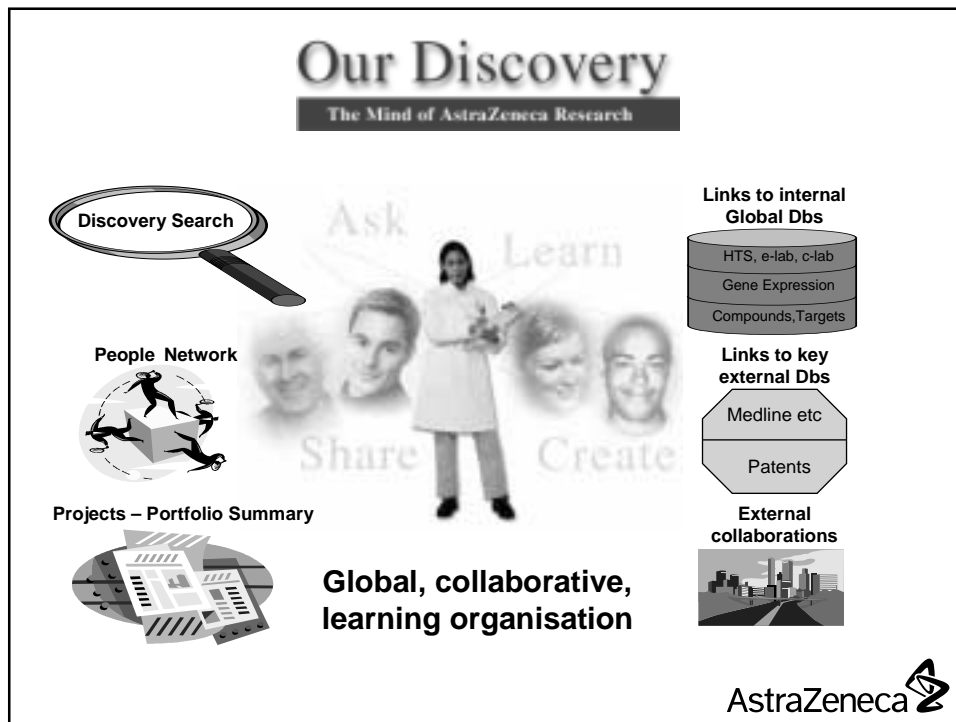


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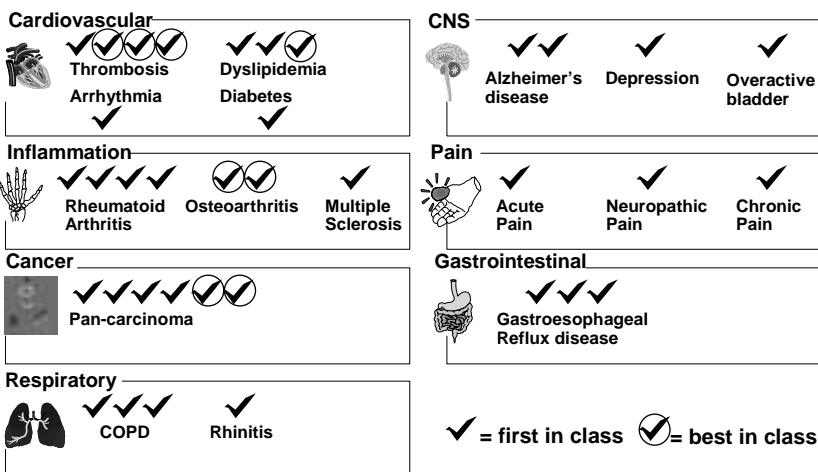
## Global working - External input to projects



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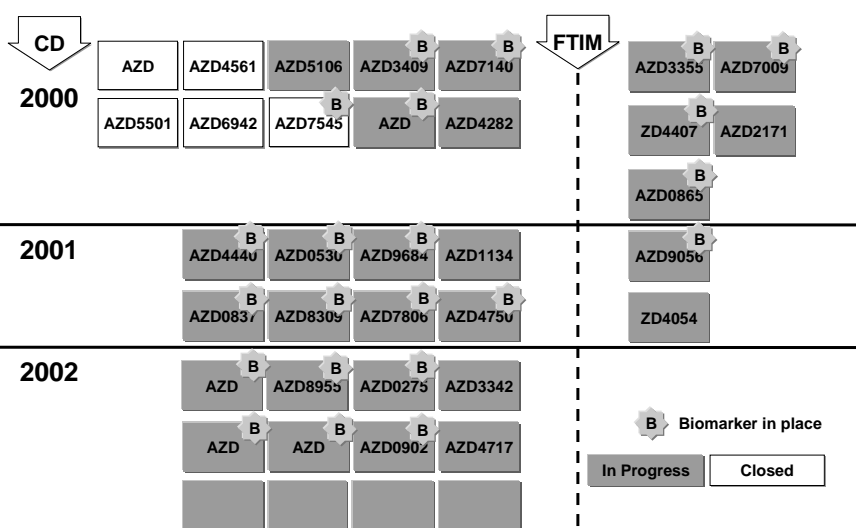


## CD delivery last 3 years



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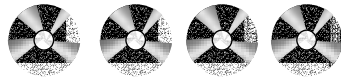
## Recent CD progress



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## Overall CD delivery and progress last 3 years

- More
  - ◆ increased CD delivery
  - ◆ increased number of CDs into man
- Better
  - ◆ quality CD criteria implemented
  - ◆ biomarkers for most CDs
- Faster
  - ◆ shorter lead optimisation
  - ◆ shorter timelines CD nomination to first time into man



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## AstraZeneca Discovery productivity

- 1 quality CD per month to preclinical development
- Improving long-term project viability by humanising discovery and front-loading evaluation of safety and DMPK
- Global working with clever integration of enabling technology and external collaborations
- Delivering novel mechanism/first-in-class projects – some with best in class
- Exploiting pan-Therapy Area potential of our CDs

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