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Challenges and Rewards in Medicinal Chemistry Targeting Cardiovascular and Metabolic Diseases

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Abstract: Medicinal chemistry has been transformed by major technological and conceptual innovations over the last three decades: structural biology and bioinformatics, structure and property based molecular design, the concepts of multidimensional optimization (MDO), *in silico* and experimental high-throughput molecular property analysis. The novel technologies advanced gradually and in synergy with biology and Roche has been at the forefront. Applications in drug discovery programs towards new medicines in cardiovascular and metabolic diseases are highlighted to show impact and advancement: the early discovery of endothelin antagonists for endothelial dysfunction (Bosentan), 11-beta hydroxysteroid dehydrogenase (11β-HSD1) inhibitors for dysregulated cellular glucocorticoid tonus (type 2 diabetes and metabolic syndrome) and non-covalent hormone sensitive lipase (HSL) inhibitors to study the scope of direct inhibition of lipolysis in the conceptual frame of lipotoxicity and type 2 diabetes.

Keywords: Cardiovascular · High-throughput screening · Medicinal chemistry · Metabolic · Molecular design

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The Art of Medicinal Chemistry

Over the last three decades medicinal chemistry has been transformed by major technological and conceptual innovations, the implementation of structural biology and bioinformatics, the accomplishments of structure and property based molecular design, the concepts of multidimensional optimization (MDO), *in silico* and experimental high-throughput molecular property analysis together with miniaturization of biological assays, the development of high-throughput screening systems of millions of molecules, the build-up of robotized compound storage facilities. Since the early 1980s Roche has been at the forefront of the new developments and has made significant investments.[1]

What is now state of the art has developed gradually and snapshots on application and advancement are highlighted in the frame of discovery programs towards new medicines in the area of cardiovascular and metabolic diseases. The programs have led to an array of advanced proof of concept molecules and the marketed new medicine Bosentan.

Endothelin Receptor Antagonists (Abnormal Vascular Tone)

The endothelins (ETs) were discovered in 1988 by Yanagisawa.[2] They are made up of a family of vasoconstrictive and mitogenic peptides, ET 1-3, are produced by endothelial cells, act in a paracrine fashion and exert their biological activity through activation of two G protein-coupled receptors, pharmacologically and structurally described as ET_A and ET_B. ET-1 has attracted considerable scientific interest due to its extremely potent and long-lasting vasoconstrictor effect mediated through the ET_A receptor subtype expressed on smooth muscle cells (Fig 1).

Elevated ET plasma levels have been associated with a variety of cardiovascular, pulmonary, renal and gastrointestinal diseases characterized by abnormal vascular tone and/or abnormal proliferation. Due to this and the powerful physiological effects of the endothelins, particularly ET-1, significant efforts have been undertaken to develop mixed or ET_A receptor selective antagonists. More than 6000 papers have been published alone in the period from their discovery up to 1996.

At Roche we started the project in 1988 and we were the first to discover and disclose low molecular weight, non-peptide endothelin receptor antagonists and elucidate the pathophysiological role of endothelin.[3]

The innovation at the time: The general opinion then was that it would constitute a major challenge to substitute a large peptide hormone by a small molecule binder (to compete for a G protein-coupled recep-

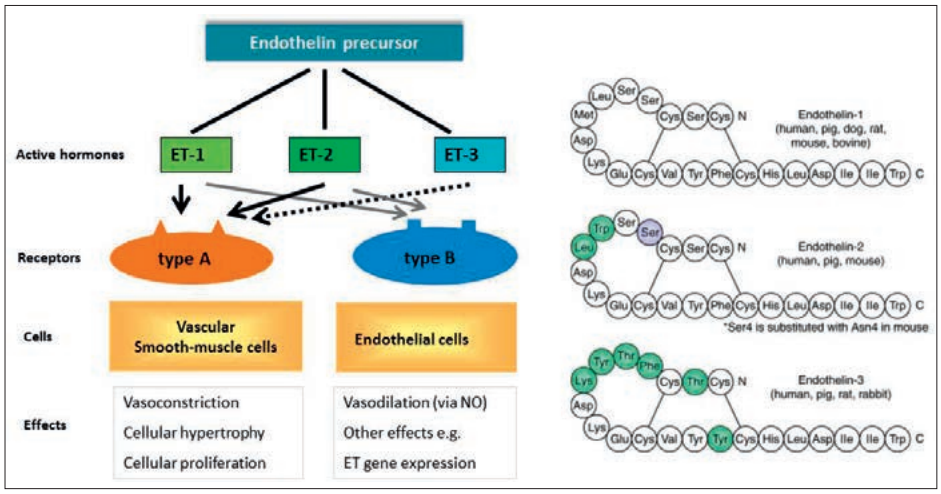

Fig. 1. The ETs and ET receptors: structure, function, tissue expression and effects.

tor). A lot of activities thus were directed to prepare peptide analogues.

However, taking into account the inherent metabolic instability of peptides, we wanted to go for orally active small molecule antagonists. As it was not thought possible to design *de novo* non-peptide ligands for GPCR coupled receptors, we chose a chemical file screening approach to identify lead structures. This was not standard at the time. The concept of high-throughput screening was just developing.

We had constructed a first prototype screening library of 100'000 molecules as mixtures of 10 and screened it for competitive binding vs. radiolabeled ET-1 on various receptor preparations (human placenta membrane) and recombinant ET_A receptor expressed in Sf9 and CHO cells. It resulted in the identification of a lead series of pyrimidine sulfonamides with micromolar activity in the binding assay, which were also functionally active, inverting ET mediated constriction of rat aortic rings with a pA2 of 5.8 (Fig. 2).

One of our early rewards was that we had the tool at hand to elucidate the role of endothelin in various preclinical models of pathological vasospasm. It indicated potential for antagonists in acute situations of cerebral vasospasm, renal ischemia but also in chronic diseases such as congestive heart failure and hypertension.

From the lead structure we then developed a whole set of improved molecules. The next step was the discovery of Bosentan in 1991.[4] It was launched as Tracleer in 2001, the first ET antagonist to reach the market.

Several follow-up programs for further improved molecules were then conducted (Fig 3). Teszosentan (RO0610612) and Clazosentan (RO0611790) were tailored for intravenous use by synthesizing additional functionality into the scaffold of Bosentan to enhance binding affinity and aqueous solubility.[5] Differentiated selectivity profiles were achieved through substitution at the *para*-pyridine sulfonamide position with Clazosentan showing affinity to ET_A receptors in the subnanomolar range and about 1000-fold selectivity for the ET_A receptors.[6] It was licensed to Axovan and has been in clinical development for subarachnoid hemorrhage. Teszosentan was licensed to Actelion in 1998 and has been investigated clinically for the indication acute heart failure. Regarding clinical compounds tailored for oral use, RO0485695 was optimized from Bosentan for a dual profile and low nanomolar binding affinities through implementation of additional functionality at the hydoxyethoxy moiety at C6 of the central pyrimidine[7] whereas Avosentan was optimized for ET_A receptor selectivity and high oral bioavailability.[8] Avosentan was licensed to Speedel in 1998 and has been investigated clinically for the indication overt diabetic nephropathy.[9]

To summarize: By making use of a first prototype screening library medicinal chemistry provided an array of differentiated molecules derived from a screening hit and tailored to study the effects of en-

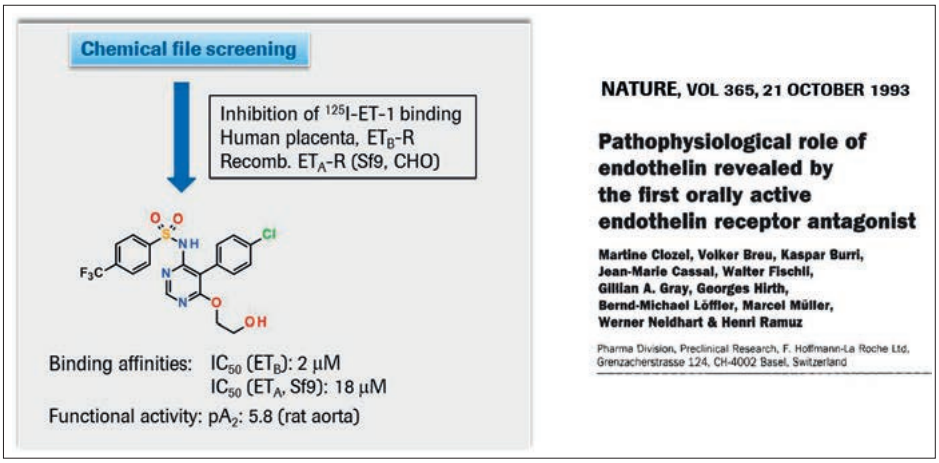

Fig. 2. Discovery of primary lead structures.

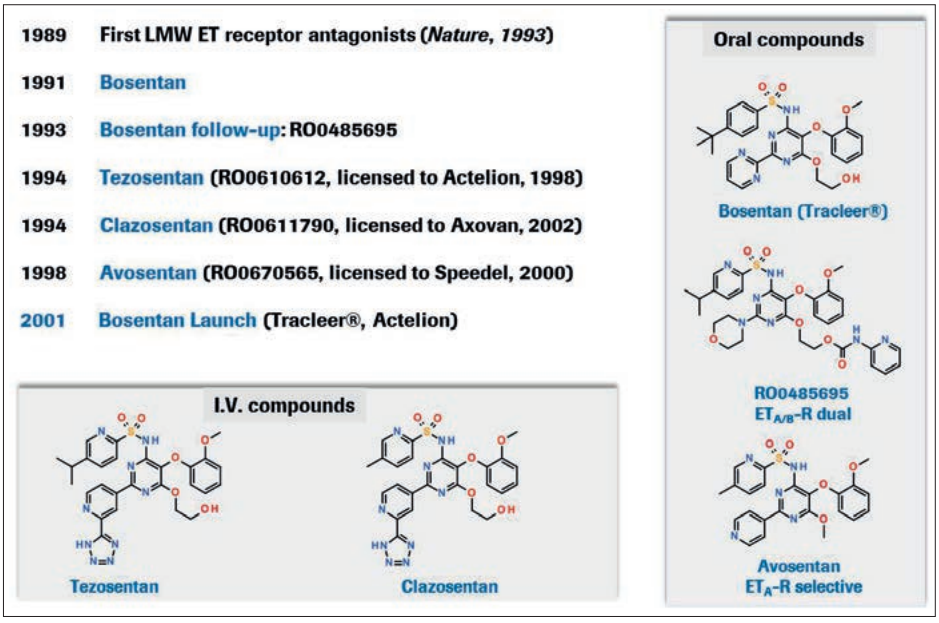

Fig. 3. Overview on the Roche endothelin program. The clinical compounds.

dothelin antagonism in pathophysiological conditions of post-ischemic vasoconstriction in acute and chronic settings. This enabled various hypotheses to be investigated and led to the marketed product Bosentan (Tracleer) for the treatment of pulmonary arterial hypertension (PAH) developed at Actelion.

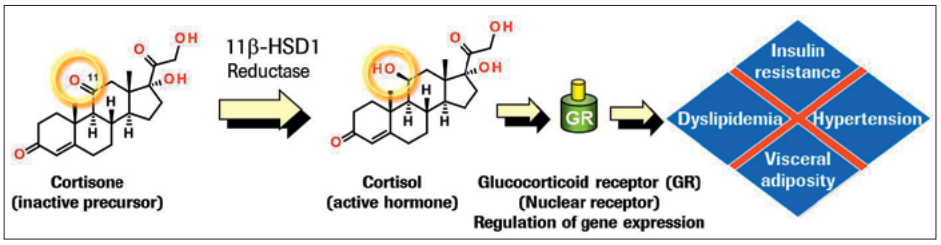

Fig. 4. Function of 11β-HSD1 as cortisone reductase. Possible implications for type 2 diabetes.

11β-HSD1 Inhibitors (Type 2 Diabetes)

I want to highlight another program, 11β-HSD, that we started in 2004 towards a new treatment paradigm for type 2 diabetes. The medicinal chemistry strategy was driven by X-ray based molecular design throughout the lead finding and optimization phase. The particular situation was that co-crystals of new molecules with the target enzyme could be obtained by crystallographic soaking enabling fast turnaround cycles. This allowed experimental binding data (IC_{50} inhibition values) to be related to protein–ligand interactions at atomic resolution and to design improved molecules with higher activity. About sixty co-crystal structures were solved during the program.

For the background: 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) is an endoplasmic reticulum-associated enzyme that acts as an NADPH-dependent reductase and converts inactive cortisone to the active glucocorticoid (GC) cortisol, a natural functional antagonist of insulin.[10] Clinical studies suggested an active role for cortisol in the pathogenesis of type 2 diabetes and data from preclinical studies (with inhibitors, 11β-HSD1 knockout mice, tissue specific overexpression in mice) had revealed that 11β-HSD1 and levels of GC production in adipose and liver tissue may play a critical role in mediating the initiation of insulin resistance and progression to diabetes.[11] This suggested that selective inhibitors of 11β-HSD1 may provide a means to treat type 2 diabetes as well as associated conditions such as dyslipidemia, hypertension, coronary heart disease, visceral adiposity (metabolic syndrome). To have an 'all in one' treatment of the multiple facets of metabolic disorders would simplify therapy (Fig. 4).

Our goal was to identify potent non-steroid inhibitors with high selectivity for 11β-HSD1 to avoid interference with steroid biosynthesis controlled by other hydroxysteroid dehydrogenases such as 11β-HSD2, 17β-HSD1/2. One of the challenges of the program was the location of 11β-HSD1, which is anchored to the inner membrane of the lumen of the endoplasmic reticulum. This would require molecules with high cell permeation properties, capable to pass multiple membranes, with high solubility and low plasma protein binding (high fraction unbound) to engage the target efficiently against a high serum albumin background at the site. Further challenges were the considerable species differences of the enzyme. The screening cascade which was set up reflected the issues; the biochemical assays were done with human, mouse and monkey enzymes, cellular assays included liver and fat cells with 0.5% bovine serum albumin. Selectivity screens comprised 11β-HSD2 and 17β-HSD1. The primary *in vivo* screen was an acute conversion assay (mouse, monkey) monitoring liver driven cortisol production (in plasma) after an exogenous cortisone challenge and oral pre-treatment with inhibitor. For sub-chronic efficacy studies diabetic (glucose, insulin sensitizing) and obese mouse models (body weight, lipids) were set-up.

X-ray complex structures of 11β-HSD1 were first published in 2005.[12] Our designs were based on X-ray co-crystal structures that we had solved in-house with some early primary lead structures obtained from the public domain[13] and through a biased screen. From the structures it was revealed that the ketone functions of the cores of the primary leads mimic the 11-keto group of cortisone, being engaged in a hydrogen bond network with Ser170 and Tyr183 of the catalytic triad and in stacking interactions with the cofactor NADP positioned above. The central core is flanked by hydrophobic substituents that engage in multiple apolar interactions in the binding site substituting for the lipophilic tetracyclic steroidal skeleton of cortisone (Fig. 5).

The progression from primary leads to clinical candidate series is outlined in Fig. 5: the key transformations being to generate scaffolds that can mimic the keto group at C11 of the hormone, build stable lipophilic volume around the core to get to molecules which are metabolically stable, neutral, small and highly soluble to reach the target efficiently.

From this strategy we quickly identified two clinical lead series, pyrazolones, RO5026856[14] and carbocyclic pyridazines, RO5027838.[15] The activity and molecular property profiles of the two molecules were within the requested thresholds (Fig. 6). For the pyrazolone RO5026856, the two cyclopropane rings were accommodating well in the 11β-HSD1 active site and provided compounds with high ligand efficiency (LE, binding energy per heavy atom) and excellent to good microsomal stability (expressed as 'MAB' values, 'maximal achievable bioavailability'). The *ortho* CF_3 substituent was found to boost potency as well as stability, with the CF_3 group making efficient hydrophobic contacts in the active site beneath the pyrazolone plane (Fig. 7).

The pyridiazines were designed to

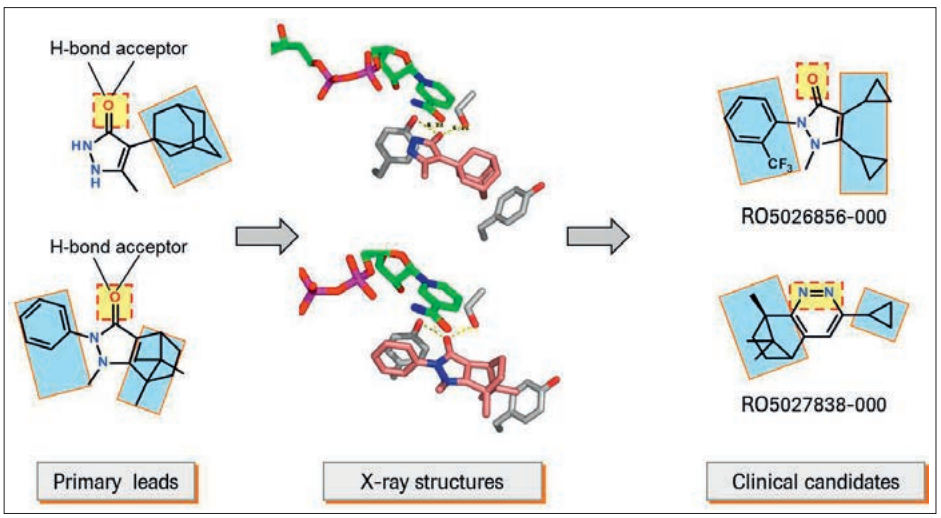

Fig. 5. Evolution of primary lead structures to clinical candidates.

translate the C=O to the N=N pharmacophore which was confirmed by the X-ray structures (Fig. 8). The carbocyclic (trimethyl-norbornyl) moiety proved to drive affinity. It filled well the enzyme active site providing stable hydrophobic volume. The binding site was large enough to accommodate rigid cage structures such as adamantyl or norbornyl resulting in low ligand entropy cost upon binding and high ligand efficiency. The cyclopropyl substituent contributed to affinity and metabolic stability. The key compounds had high *in vitro* human activity (mouse activity was typically lower) and good MDO properties (BCS class 1). In human liver microsomes the compounds were generally stable with rodent stability typically lower (driven by the bicyclic part). Reducing lipophilicity at this site (*e.g.* norbornane) improved mouse stability but led to a reduction in binding affinity.

Both molecules were advanced as clinical candidates without stop signals. They differentiated with respect to structure, tissue distribution and PK properties (volume of distribution, Vss, and plasma protein binding, fu).

From this program RO5027838 entered clinical trials. It was selected due to its tissue selectivity, adipose over liver. The molecule was well tolerated. In a phase 2 study in metformin-treated patients with type 2 diabetes over 28 days it showed inhibitory effects on 11β-HSD1 activity based on urinary corticosteroid excretion. The molecule showed a trend for improved HbA1c levels and consistent reduction of body weight exceeding that observed with placebo. Insulin sensitivity parameters did not improve in this study.[16]

To summarize: A knowledge and information driven design approach with direct access to X-ray co-crystals of inhibitor enzyme complexes provided swiftly two differentiated clinical lead series with the molecular and pharmacokinetic properties tailored for the particular localization of the target enzyme. This enabled to test the concept of inhibition of 11β-HSD1 in the frame of type 2 diabetes and associated risk factors (the metabolic syndrome) in a clinical setting.

		RO5027838	RO5026856
Permeation log D / Solubility		Flux 8 ($10e^{-6}$ cm/s) 2.7 / 1200 µg/ml	Flux 9 ($10e^{-6}$ cm/s) 2.2 / 634 µg/ml
Ligand efficiency, LE		0.59 kcal/mol/atom	0.47 kcal/mol/atom
Efficacy	Enzym-hum +BSA (IC_{50})	0.05 µM (monkey 1.2 µM)	0.01 µM (monkey 0.035 µM)
	Cells-hum H4Ile (EC_{50})	0.06 µM	0.01 µM
	Cells-mo L1 (EC_{50})	0.135 µM (mo H4Ile 0.19 µM)	0.22 µM (mo H4Ile 0.25 µM)
Stability	Micr. Stab. – human	81% MAB	92% MAB
	- mouse	28% MAB	50% MAB
Safety	DDI (CYPs, IC_{50})	>50 µM (3A4,2C9,2D6)	>50 µM (3A4,2C9,2D6)
	hERG (% inhib)	14% (at 10 µM)	5% (at 10 µM)
	Ames / MNT (Cerep)	Negative (Cerep no issues)	Negative (Cerep no issues)
Prot-bg	Fu (%)	Mouse 22, hum 28	Mouse 4, hum 18

Fig. 6. *In vitro* activity and MDO profiles of key molecules.

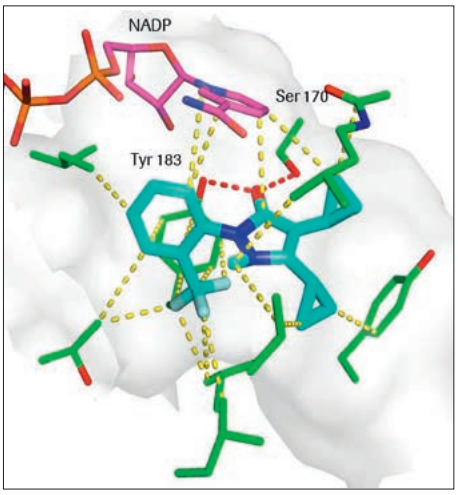

Fig. 7. X-ray co-crystal structure of RO5026856, NADP and human 11β-HSD1 (Resolution: 2.1 Å). Key interactions are shown as dashed lines (red: hydrogen bonds, yellow: hydrophobic).

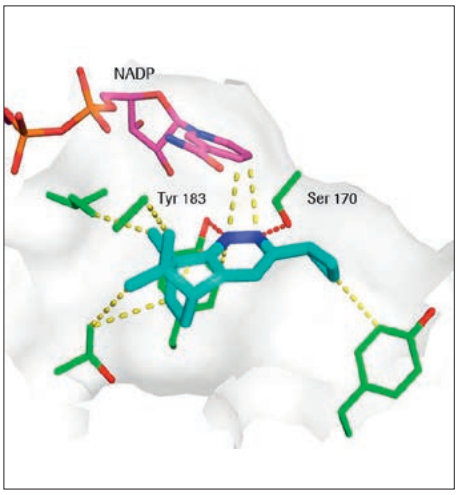

Fig. 8. X-ray co-crystal structure of RO5027838, NADP and human 11β-HSD1 (Resolution: 2.8 Å). Key interactions are shown as dashed lines (red: hydrogen bonds, yellow: hydrophobic).

Hormone Sensitive Lipase (HSL)

The HSL program is highlighted as a further case study. The project was started in 2008. It was driven by a high-throughput screening for primary hits and a lead optimization program based on homology modeling, which resulted in the discovery of first-in-class, non-covalent (non-acylating) and reversible HSL inhibitors.

What was the underlying rational for targeting HSL? Hormone sensitive lipase (HSL) is an intracellular neutral serine lipase/esterase and highly expressed in adipose tissue where it controls release of free fatty acids from triacylglycerides (TAG) upon extracellular hormonal stimulus[17] (Fig. 9). Its natural substrate is diacylglycerol (DAG). As such, it is a regulator of adipocyte lipolysis and it has been shown that type 2 diabetic individuals exhibit enhanced lipolytic activity due to up-regulation of HSL.[18] There is evidence that this chronic increase of plasma levels of free fatty acids further aggravates insulin resistance. This is likely driven by accumulation of triglycerides in tissues other than white adipose tissue such as liver, pancreas and muscle causing pathological damage, lipotoxicity and diabetes. Therefore it was hypothesized that pharmacological inhibition of HSL may restore exaggerated plasma free fatty acid and triglyceride levels and be of therapeutic value for the treatment of type 2 diabetes.

Our goal was to go for a first-in-class inhibitor profile, unique for this type of serine lipases. We wanted to achieve small molecule competitive, reversible inhibitors of the lipase with good PK properties enabling study of the effect of direct inhibition of lipolysis in proof of concept studies in the frame of lipotoxicity and type 2 diabetes. HSL inhibitors studied so far were metal electrophiles[19] and reactive acylators, pseudo-substrates[20] that modify the enzyme active site in a time-dependent manner and can raise safety concerns.

One of the early assets of the program was the construction of a homology model of human and rat HSL. It was built using a HSL template structure from PDB 3dnm which was obtained from screening a metagenome library.[21] The structure of the template was determined at a resolution of 2.8 Å. It shares 24% sequence identity with human HSL. Related enzymes with a highly conserved fold like a carbo-

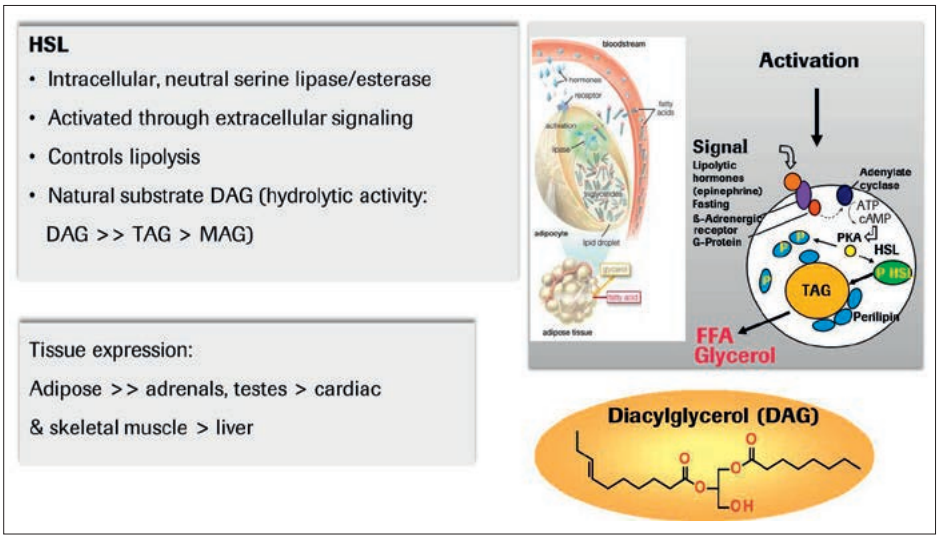

Fig. 9. The role of HSL in the mechanism of hormone stimulated lipolysis.

xylesterase from Archaeon Archaeoglobus or Brefelding A esterase also share 20 and 25% sequence identity with PDB 3dnm. Binding modes for compounds from the HTS as well as from the lead series were then established. Several experimental observations, *e.g.* differences in activity for human and rat HSL could be explained and were used to validate the homology model. The model also allowed predictions on regioselectivity in the lead series and was validated with experimental data.

The lead finding started with an high-throughput screening of about 900'000 compounds with a fast *in vitro* assay developed for this purpose (and cross-checked against natural substrates), dimercapto-1-propanol tributyrate as substrate, monitoring conversion to free fatty acid and glycerol-SH in an absorbance assay format. It gave rise to a primary hit rate of 2.7%. Dose-response curves, IC_{50} values and selectivity ratios vs. other esterases, lipases such as cholesterol esterase (CE), acetylcholine esterase (ACE) were obtained for about 9'000 confirmed hits. The confirmed hits were subjected to substructure clustering and interactive data analysis was carried out using potency and selectivity thresholds (IC_{50} *ca.* < 0.5 µM, ACE & CE select >50 µM), calculated physicochemical properties (molecular weight, lipophilicity, clog P), lead-like alerts, screening exclusion flags, ligand efficiency, ratio ligand efficiency/surface binding efficiency and comparative HTS analysis ('frequent hitters'). Clusters comprising putative acylating, alkylating, pseudo-substrate functionality (being reactive to the enzyme) were discarded. From the prioritized clusters a key set of *ca.* 135 potent (enzyme assay) and selective compounds were chosen for in-depth evaluation comprising advanced selectivity and cell assays, MDO (log D, solubility), *in vitro* PK (microsomal stability) and toxicity assays (hERG activity, Ames, MNT, covalent binding liabilities).

The advanced selectivity assays comprised a range of relevant esterases and lipases to address potential toxicity issues, *i.e.* cholesterol esterase (CE), acetylcholine esterase (ACE) together with a number of functionally related lipases as adipose triglyceride lipase (ATGL), lipoprotein lipase (LPL), hepatic lipase (HL) and pancreatic lipase (PL). Further, a relevant cell assay had been set-up, measuring forskolin induced lipolysis in mouse adipocytes. An acute *in vivo* model was developed, monitoring plasma free fatty acids in over-night fasted obese mice after an oral challenge with inhibitor. A sub-chronic model was set up in diet-induced obese mice (DIO) with insulin sensitizing effects (OGTT, glucose) as read-outs.

The evolution of the HTS hit RO4950511 from a cluster of piperidine carboxylic acid amides to the spiropiperidine primary lead series,[22] *i.e.* RO5434227, is illustrated in Fig. 10. The key transformation was a spiro-cyclization from the amide to the central core which led to metabolically stable molecules with enhanced binding affinity through the entropic term. Key molecules, *i.e.* RO5434227, were *in vivo* active, did show good PK profiles and had no *in vitro* toxicity flags. In enzyme kinetics studies, competitive and reversible binding features were confirmed, which was in line with homology modeling and as expected from the structure.

The anticipated binding mode of RO5434227 in the homology model is shown in Fig 11.

The key interactions being: the carbonyl group of the spiroamide is located in the oxyanion hole and stabilized *via* hydrogen bonding with the catalytic serine shown behind marked in yellow. The right side N-aryl group of RO5434227 reaches into

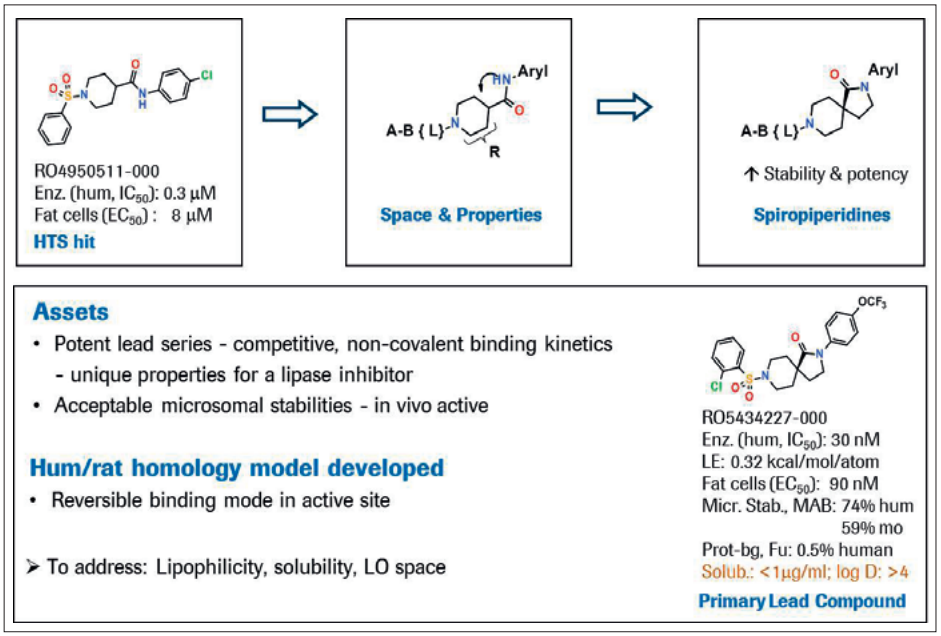

Fig. 10. Lead generation. From HTS hits to primary lead series, spiropiperidines.

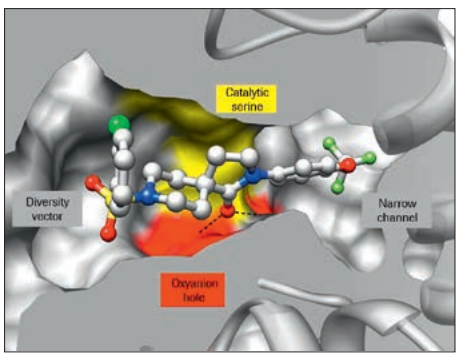

Fig. 11. Homology model of human HSL with binding hypothesis for RO5434227.

a narrow hydrophobic channel (accommodating in DAG the C1 fatty acid which is cleaved-off by the enzyme). Flanking backbone carbonyls are accessed for directed interactions. The aryl sulfonamide part of RO5434227 is located in a solvent exposed area of the lipase and interactions with hydrophobic patches are picked up.

The lead structure constitutes a translational mimetic of DAG, the spiropiperidine core mimicking the glycerol backbone, defining exit vectors, providing a stable carboxamide functionality for interaction in the oxyanion hole and positioning the N-aryl effectively into the narrow lipophilic channel occupied by the C1 fatty acid in DAG.

The model suggested space for broad modifications to the left (diversity vector) to tune the MDO properties (solubility and log D) whereas the right side of the binding pocket was defined and specific, suggesting molecular design to refine potency.

The already advanced series was further developed following the modeling hypotheses. Main goals were to broaden molecular space, balance affinity vs. lipophilicity and increase aqueous solubility. This gave then rise to the clinical lead series of tertiary hydroxy spirocyclohexanes which had broad scope and further improved properties[23] (Fig 12).

The key transformation was to move the nitrogen out of the ring and engineer additional hydrogen bond donor acceptor interactions to an active site glutamine residue close to the oxyanion hole through a *syn* hydroxy group from the spirocyclohexane core. This gave rise to molecules with higher ligand efficiency. It allowed high affinities to be achieved with more compact and smaller molecules, compensating for the larger aryl sulfonamide part, with lower lipophilicity (log D) and better solubility. It opened up molecular space, and from the first prototype molecule RO5472857 a whole set of improved compounds was derived through refinement of the substituents of which RO5519390 was profiled as one of the candidate molecules for pre-clinical POC studies. The molecule had a balanced lipophilicity and acceptable aqueous solubility. It was potent in enzyme and cell assays with high metabolic stability (high MAB values). It did not have flags in regard to the *in vitro* safety (hERG: IC_{50} >50 μM, IC_{20} 7.4 μM).

The molecule was active *in vivo* in the acute assay and lowered plasma free fatty acids at a dose of 3 mg/kg in over-night fasted obese mice after an oral challenge with inhibitor.

RO5519390 was tested in the 21-day sub-chronic studies in mice at 5 mg/kg per day, with an insulin sensitizer (rosiglitazone = Avandia, a PPAR agonist) as positive control and against vehicle. The endpoints of measurement were insulin sensitization (insulin levels, insulin at oGTT), plasma glycerol and free fatty acids, plasma and liver triglycerides, gene markers in white adipose tissue (WAT). The results were very positive; the molecule showed very favorable efficacies at low doses and was chosen as shortlist clinical candidate. It showed significant effects on improving insulin sensitivity and fat metabolism, a trend to decrease bodyweight without affecting food intake (FI). Further, epididymal fat pad weight as well as liver weight was reduced. The HSL inhibitor was differentiated from an insulin sensitizer (rosiglitazone) in terms of pharmacodynamic effects and white adipose tissue (WAT) gene expression pathways.

In regard to clinical chemistries, there were no significant changes in liver plasma enzymes but a trend to increased basal corticosterone levels.

Further pre-clinical data in regard to drugability of HSL for diabetes, will be published separately.

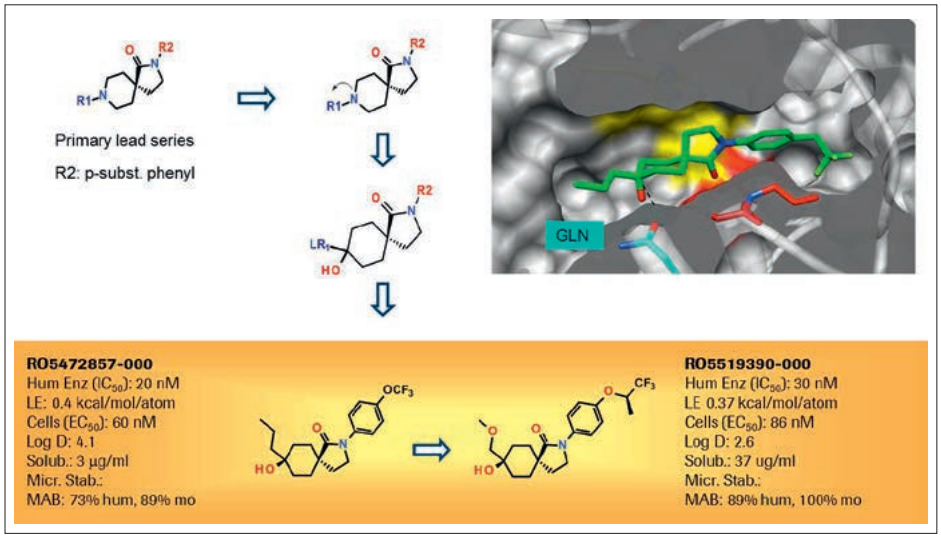

Fig. 12. Lead refinement. Towards the key series of tertiary hydroxy spirocyclohexanes.

To summarize: first-in-class, non-covalent (non-acylating) competitive, non-covalent HSL inhibitors were generated from an HTS hit through molecular design. Key compounds are highly selective with nanomolar enzyme and cell potencies and favorable pharmacokinetic properties. High acute and sub-chronic efficacy was demonstrated with optimized candidate molecules in models of type 2 diabetes. The HSL inhibitors were differentiated from insulin sensitizers in terms of pharmacodynamic effects and white adipose tissue (WAT) gene expression pathways.

The new molecules enabled the study of the effects and scope of direct inhibition of lipolysis in the conceptual frame of lipotoxicity and diabetes.

Conclusion

The rapid evolution of novel technologies has created new avenues in medicinal chemistry. However, the identification, synthesis and development of new medicines for therapeutic use remain a big challenge. A wide range of expertise developed through years of dedication and learning from best practices is required to bring a new molecule in clinical development and a new therapy to market.

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